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(21) International Application Number: PCT/US99/12366 (22) International Filing Date: 6 July 1999 (06.07.99) (30) Priority Data: <table border="0"> <tr> <td>09/110,938</td> <td>6 July 1998 (06.07.98)</td> <td>US</td> </tr> <tr> <td>09/114,466</td> <td>13 July 1998 (13.07.98)</td> <td>US</td> </tr> <tr> <td>60/093,897</td> <td>23 July 1998 (23.07.98)</td> <td>US</td> </tr> <tr> <td>09/132,968</td> <td>12 August 1998 (12.08.98)</td> <td>US</td> </tr> <tr> <td>09/136,214</td> <td>18 August 1998 (18.08.98)</td> <td>US</td> </tr> <tr> <td>60/099,999</td> <td>11 September 1998 (11.09.98)</td> <td>US</td> </tr> </table> (71) Applicant: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US). (72) Inventors: BATES, Elizabeth, Esther, Mary; 4, place Gabriel Rambaud, F-69001 Lyon (FR). LEBECQUE, Serge, J., E.; 514, Chemin du Marand, F-69380 Civrieux d'Azergue (FR). MURPHY, Erin, E.; 180 Emerson Street, Palo Alto, CA 94301 (US). MATTSON, Jeanine, D.; 559 Alvarado Street, San Francisco, CA 94114 (US). GORMAN, Daniel, M.; 6371 Central Avenue, Newark, CA 94560 (US). HEDRICK, Joseph, A.; 52-08 Quail Ridge Drive, Plainsboro, NJ 08536 (US). WANG, Luquan; 21 Hollis Road, East Brunswick,		09/110,938	6 July 1998 (06.07.98)	US	09/114,466	13 July 1998 (13.07.98)	US	60/093,897	23 July 1998 (23.07.98)	US	09/132,968	12 August 1998 (12.08.98)	US	09/136,214	18 August 1998 (18.08.98)	US	60/099,999	11 September 1998 (11.09.98)	US	NJ 08816 (US). ZLOTNIK, Albert; 507 Alger Drive, Palo Alto, CA 94306 (US). MURGOLO, Nicholas, J.; 99 Rolling Hill Drive, Millington, NJ 07946 (US). GREENE, Jonathan, R.; 457 Tillou Road, South Orange, NJ 07079 (US). JOHNSTON, James, A.; 205 Mary Alice Drive, Los Gatos, CA 95032 (US). BAZAN, Jose, Fernando; 775 University Drive, Menlo Park, CA 94025 (US). MAHONY, Daniel; 330 East 39th Street #21-A, New York, NY 10016 (US). LEES, Emma, M.; 3107 Washington Street, San Francisco, CA 94115 (US). (74) Agents: THAMPOE, Immac, J. et al.; Schering-Plough Corporation, Patent Dept., K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MD, MG, MK, MN, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). <p style="text-align: center;">Published Without international search report and to be republished upon receipt of that report.</p>
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(54) Title: MAMMALIAN GENES; DENDRITIC CELL PROSTAGLANDIN-LIKE TRANSPONDER (DC-PGT), HDTEA84, HSLJD37R AND RANKL, HCC5 CHEMOKINE, DEUBIQUITINATING 11 AND 12 (DUB11, DUB12), MD-1, MD2 AND CYCLIN E2, RELATED REAGENTS AND METHODS (57) Abstract Purified genes from a mammal, reagents related thereto including purified proteins, specific antibodies, and nucleic acids encoding the polypeptides are provided. Methods of using said reagents and diagnostic kits are also provided. Characterization of genes and products relating to DC-PGT (Dendritic cell prostaglandin-like transporter), HDTEA84, HSLJD37R and RANKL (related to TNF receptor family), HCC5 chemokine, Dub 11 and Dub 12 (Deubiquitinating 11 and 12), MD-1 and MD-2 (proteins which exhibit properties of ligands for proteins exhibiting a leucine-rich protein motif (LRR)) and cyclin E2.																				

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MAMMALIAN GENES; DENDRITIC CELL PROSTAGLANDIN-LIKE TRANSPONDER (DC-PGT), HDTEA84, HSLJD37R AND RANKL, HCC5 CHEMOKINE, DEUBIQUITINATING 11 AND 12 (DUB11, DUB12), MD-1, MD2 AND CYCLIN E2. RELATED REAGENTS AND METHODS

FIELD OF THE INVENTION

5 The present invention pertains to compositions related to
proteins which: function in cellular physiology, development, and
differentiation of mammalian cells; exhibit sequence similarity to
TNF receptors which function in controlling activation and
expansion of mammalian cells, e.g., cells of a mammalian immune
10 system; or function in controlling the cell cycle and growth. In
particular, it provides purified genes, proteins, antibodies, and
related reagents useful, e.g., to separate or identify particular
cell types, or to regulate activation, development,
differentiation, and function of various cell types, including
15 hematopoietic cells; which exhibit high structural similarity to
proteins that exhibit the biological capacity to serve as a
carrier mediated transporters of charged organic anions across
cellular membranes, which typically can be used in prostaglandin
and thromboxane physiology, e.g., transportation, influx, efflux,
20 clearance, or degradation; which regulate or evidence development,
differentiation, and function of various cell types, including
hematopoietic cells; or to regulate cell division and
proliferation of various cell types, including tumor cells.

25 BACKGROUND OF THE INVENTION

Prostaglandins (PGs) and thromboxanes (TXs) play widespread physiological, and therapeutic roles in health and disease such as glaucoma; pregnancy, labor, delivery, and abortion; gastric protection and peptic ulcer formation; intestinal fluid secretion; liver protection and damage; airway resistance and asthma; blood pressure control; and modulation of inflammatory cells.

PGs are charged anions at physiological pH that diffuse poorly across biological membranes. This limited simple diffusion appears to be augmented by carrier mediated transport in many diverse tissues such as the lung, choroid plexus, liver, anterior chamber of the eye, vagina, uterus, and placenta.

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Understanding the role of prostaglandins in the development and functioning of the immune system is presently incomplete. Specifically, the influence of prostaglandins (PGs) on antigen presenting cells (APCs) of the immune system (e.g., dendritic cells) is, as yet, poorly understood.

Dendritic cells (DCs) are the most potent of antigen presenting cells. See, e.g., Paul (ed. 1993) Fundamental Immunology 3d ed., Raven Press, NY. DCs are highly responsive to inflammatory stimuli such as bacterial lipopolysaccharides (LPS) and cytokines such as tumor necrosis factor alpha (TNF α). The presence of cytokines and LPS can induce a series of phenotypic and functional changes in DC that are collectively referred to as maturation. See, e.g., Banchereau and Schmitt Dendritic Cells in Fundamental and Clinical Immunology Plenum Press, NY.

Maturation changes in DCs include, e.g., silencing of antigen uptake by endocytosis, upregulation of surface molecules related to T cell activation, and active production of a number of cytokines including TNF α and IL-12. Upon local accumulation of TNF α , DCs migrate to the T cell areas of secondary lymphoid organs to activate antigen specific T cells.

Recent data indicate that DCs secrete PGs. See, e.g., Cormann, et al. (1986) Ann. Inst. Pasteur 137:369-382. Furthermore, PGE₂ has been shown to have an influence on DC maturity and the production of cytokines by DCs. See e.g., Kalinski, et al. (1997) J. Immunol. 159:28-35; Kuhn, et al. (1997) Eur. J. Immunol. 27:3135-3142; and Rieser, et al. (1997) J. Exp. Med. 186:1603-1608.

Currently, a need exists to understand the manner in which PGs influence cells of the immune system. It seems likely that PGs, like cytokines, effect immune system development and activation. The present invention contributes to satisfying that need and is directed generally to a novel mammalian gene encoding a prostaglandin-like transporter (PGT).

In other aspects, the activation of resting T cells is critical to most immune responses and allows these cells to exert

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their regulatory or effector capabilities. See, e.g., Paul (ed. 1993) Fundamental Immunology 3d ed., Raven Press, N.Y. Increased adhesion between T cells and antigen presenting cells (APC) or other forms of primary stimuli, e.g., immobilized monoclonal antibodies (mAb), can potentiate the T-cell receptor signals. T-cell activation and T cell expansion depends upon engagement of the T-cell receptor (TCR) and co-stimulatory signals provided by accessory cells. See, e.g., Jenkins and Johnson (1993) Curr. Opin. Immunol. 5:361-367; Bierer and Hahn (1993) Semin. Immunol. 5:249-261; June, et al. (1990) Immunol. Today 11:211-216; and Jenkins (1994) Immunity 1:443-446. A major, and well-studied, co-stimulatory interaction for T cells involves either CD28 or CTLA-4 on T cells with either B7 or B70 (Jenkins (1994) Immunity 1:443-446). Recent studies on CD28 deficient mice (Shahinian, et al. (1993) Science 261:609-612; Green, et al. (1994) Immunity 1:501-508) and CTLA-4 immunoglobulin expressing transgenic mice (Ronchese, et al. (1994) J. Exp. Med. 179:809-817) have revealed deficiencies in some T-cell responses though these mice have normal primary immune responses and normal CTL responses to lymphocytic choriomeningitis virus and vesicular stomatitis virus. As a result, both these studies conclude that other co-stimulatory molecules must be supporting T-cell function. However, identification of these molecules which mediate distinct costimulatory signals has been difficult.

Tumor Necrosis Factor (TNF) is the prototypic member of an emerging family of cytokines that function as prominent mediators of immune regulation and the inflammatory response. These ligands are typically type II membrane proteins, with homology at the carboxy terminus. A proteolytic processed soluble protein often is produced. See, e.g., Smith, et al. (1994) Cell 76:959-962; Armitage (1994) Current Opinion in Immunology 6:407-413; Gruss and Dower (1995) Blood 85:3378-3404; Wiley, et al. (1995) Immunity 3:673-682; and Baker and Reddy (1996) Oncogene 12:1-9. Crucial roles for these family members are evidenced by a number of studies, and they are implicated in regulation of apoptosis, peripheral tolerance, Ig maturation and isotype switching, and

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general B cell and T cell functions. See, e.g., Thomson (ed. 1994) The Cytokine Handbook Academic Press, San Diego, CA; Naismith and Sprang (1998) Trends Biochem. Sci. 23:74-79; Lucas, et al. (1997) J. Leukoc. Biol. 61:551-558; Reddi (1997) Cell 5 89:159-161; Van Deventer (1997) Gut 40:443-448; Jablonska (1997) Postepy. Hig. Med. Dosw. 51:567-575; Hill and Lunec (1996) Mol. Aspects Med. 17:455-509; Aderka (1996) Cytokine Growth Factor Rev. 7:231-240; Lotz, et al. (1996) J. Leukoc. Biol. 60:1-7; and Gruss and Dower (1995) Cytokines Mol. Ther. 1:75-105. These imply
10 fundamental roles in immune and developmental networks relevant to human therapeutic needs. The identification of ligands and cell surface receptors allow determination of pairs, which will be useful in modulating such signal transduction.

The discovery of new cell markers is always potentially
15 useful. Moreover, the inability to modulate activation signals prevents control of inappropriate developmental or physiological responses in the immune system. The present invention provides at least one alternative costimulatory molecule, which will be useful as a marker for cell types, and agonists and antagonists of which
20 will be useful in modulating a plethora of immune conditions or responses.

The circulating component of the mammalian circulatory system comprises various cell types, including red and white blood cells of the erythroid and myeloid cell lineages. See, e.g., Rapaport
25 (1987) Introduction to Hematology (2d ed.) Lippincott, Philadelphia, PA; Jandl (1987) Blood: Textbook of Hematology, Little, Brown and Co., Boston, MA.; and Paul (ed. 1993) Fundamental Immunology (3d ed.) Raven Press, N.Y.

For some time, it has been known that the mammalian immune
30 response is based on a series of complex cellular interactions, called the "immune network." Recent research has provided new insights into the inner workings of this network. While it remains clear that much of the response does, in fact, revolve around the network-like interactions of lymphocytes, macrophages,
35 granulocytes, and other cells, immunologists now generally hold the opinion that soluble proteins, known as lymphokines,

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cytokines, or monokines, play a critical role in controlling these cellular interactions. Thus, there is considerable interest in the isolation, characterization, and mechanisms of action of cell modulatory factors, an understanding of which should lead to significant advancements in the diagnosis and therapy of numerous medical abnormalities, e.g., immune system and other disorders.

Lymphokines apparently mediate cellular activities in a variety of ways. They have been shown to support the proliferation, growth, and differentiation of the pluripotential hematopoietic stem cells into vast numbers of progenitors comprising diverse cellular lineages making up a complex immune system. These interactions between the cellular components are necessary for a healthy immune response. These different cellular lineages often respond in a different manner when lymphokines are administered in conjunction with other agents.

The chemokines are a large and diverse superfamily of proteins. The superfamily is subdivided into two classical branches, based upon whether the first two cysteines in the chemokine motif are adjacent (termed the "C-C" branch), or spaced by an intervening residue ("C-X-C"). A more recently identified branch of chemokines lacks two cysteines in the corresponding motif, and is represented by the chemokines known as lymphotactins. Another recently identified branch has three intervening residues between the two cysteines, e.g., CX3C chemokines. See, e.g., Schall and Bacon (1994) Current Opinion in Immunology 6:865-873; and Bacon and Schall (1996) Int. Arch. Allergy & Immunol. 109:97-109.

Because the physiology mediated by these soluble molecules is so important, the discovery of novel chemokines will be important, both in diagnostic and therapeutic contexts.

In addition, while the general importance of the regulation of protein synthesis is universally accepted, the general importance of protein degradation has not been fully appreciated. One mechanism of protein degradation is via ubiquitination signals and degradation pathways. Ubiquitin (Ub) is a highly conserved 76 amino acid polypeptide that plays an important role in the regulation of protein degradation, cell-cycle progression, gene

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transcription and signal transduction. The ubiquitination pathway is fine tuned and controlled, in part, by deubiquitination enzymes, which remove ubiquitin from proteins. Misregulation of the ubiquitination pathway may contribute problems in the protein quantity regulation, which may be associated, e.g., with malignant transformation, and oncogenesis through oncogenic counterparts of normally processed ubiquitinated proteins. Other clinical problems will often result from excessive or insufficient protein levels. Therefore, understanding the ubiquitination roles, e.g., in immune function, will increase our understanding of cell biology, which should have relevance, e.g., to malignant transformation.

Furthermore, growth of normal resting B cells (also referred to as "B lymphocytes") involves two distinct steps. First, the resting cells are activated to pass from the G₀ to G₁ phase of the cell cycle. See, e.g., Alberts, et al. (eds. 1989) Molecular Biology of the Cell Garland Publ., NY; and Darnell, et al. (1990) Molecular Cell Biology Freeman, NY. Next, the activated cells are induced to proliferate. See, e.g., Paul, ed. (1989) Fundamental Immunology, 2nd ed., Raven Press, NY; and the third edition. Several factors have been identified that induce growth of B cells, including interleukin-1 (IL-1), IL-2, IL-4, IL-10, and IL-13. In addition, antibodies against certain B cell surface molecules have been demonstrated to promote B cell proliferation. T cells (also referred to as "T lymphocytes") are also induced to proliferate by certain factors, which include phytohemagglutinin, anti-T cell receptor monoclonal antibodies, anti-CD3 monoclonal antibodies, and other agents.

B7 (CD80) and B70 (CD86) are the second "group" of molecules which strongly mediate B and T cell interaction. These molecules, on B cells, interact with their ligands CD28 and CTLA-4 on T cells. These interactions are major co-stimulatory signals for activation of both B and T cells.

During the last 15 years, it has become apparent that B7 (CD80) and B70 (CD86) play fundamental functions in T cell and B cell activation. Numerous in vitro and in vivo experiments have demonstrated that these two pairs of molecules represent important

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targets for immunosuppression. See, e.g., Banchereau, et al. (1994) Ann. Rev. Immunol. 12:881-922; van Kooten, et al. (1996) Adv. Immunol. 61:1-77; Linsley and Ledbetter (1993) Ann. Rev. Immunol. 11:191-212).

5 In 1995, another molecule called RP105 was cloned from mouse splenic cells. See Miyake, et al (1995) J. Immunol. 154:3333-3340. Monoclonal antibodies against RP105 also induce strong proliferation of mouse B cells and protects mouse B cells from irradiation-induced apoptosis in a similar fashion to anti-CD40
10 antibody or CD40-ligand. See Miyake, et al. (1994) J. Exp. Med. 180:1217-1224.

The RP105 molecule and its ligand MD-1 may be an additional pair of molecules that play key roles in the activation of T cells and B cells. See Miyake, et al. (1998) J. Immunol. 161:1349-1353;
15 and Chan, et al., (1998) J. Exp. Med. 188:93-101 However, the human sequence of MD-1, has remained undetermined. The present invention provides this and also provides a previously undescribed second human homolog of mouse MD-1, (i.e., MD-2).

Many factors have been identified which influence the
20 differentiation process of precursor cells, or regulate the physiology or migration properties of specific cell types. These observations indicate that other factors exist whose functions in immune function were heretofore unrecognized. These factors provide for biological activities whose spectra of effects may be
25 distinct from known differentiation or activation factors. The absence of knowledge about the structural, biological, and physiological properties of the regulatory factors which regulate cell physiology in vivo prevents the modulation of the effects of such factors. Thus, medical conditions where regulation of the
30 development or physiology of relevant cells is required remains unmanageable.

Thus, significant therapeutic needs exist in the areas of cytokine regulation of physiology, protein degradation, and B cell signaling. The present invention provides important insights and
35 developments in these areas.

Cancer can occur in many tissues of the body. It results from a change in certain cells that causes them to evade the

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normal growth limiting mechanisms, e.g., to escape the feedback controls that normally stop cellular growth and reproduction after a given number of such cells have developed. Cell division and transcription are highly coordinated processes that play important roles in this feedback control. See, e.g., Beeson, et al. (eds. 1979) Textbook of Medicine, 15th ed., W.B. Saunders Co., Philadelphia, PA.; DeVita, et al. (eds. 1997) Cancer: Principles and Practice of Oncology, 5th ed., Lippincott, Philadelphia, PA; Neal and Hoskin (1997) Clinical Oncology: Basic Principles and Practice Oxford University Press, NY; Kastan (1997) Checkpoint Controls and Cancer CSH Press, NY; and Thomas (ed. 1996) Apoptosis and Cell Cycle Control in Cancer: Basic Mechanisms and Implications for Treating Malignant Disease BIOS Scientific, Oxford.

Molecules which function to regulate cell division play important roles in the controlled growth of various types of cells. Aberrations in these controls can lead to various disease states, e.g., oncogenesis, improper wound healing, developmental abnormalities, and metabolic problems.

The cell cycle can be divided into four phases: the presynthetic phases (G_0 and G_1); the phase of DNA synthesis (S); and the postsynthetic phase (G_2). See, e.g., Guyton (ed. 1976) Textbook of Medical Physiology, 5th ed., W.B. Saunders Co., Philadelphia, PA.; Alberts, et al. (eds. 1994) Molecular Biology of the Cell, 3rd ed., Garland Publishing, New York, NY; and Darnell, et al. (eds. 1990) Molecular Cell Biology, 2nd ed., W.H. Freeman, New York, NY. Effective chemotherapeutic agents are often those which target diseased cells in the S phase, e.g., choriocarcinoma, acute lymphocytic leukemia, lymphocytic lymphosarcoma, Burkitt's lymphoma, Hodgkin's disease, testicular neoplasms, Wilm's tumor, and Ewing's sarcoma. Unfortunately, oncogenic cells not actively dividing are less sensitive to these agents.

The lack of knowledge regarding the control of the cell cycle has hampered the ability of medical science to specifically regulate cell division or immune responses. The present invention

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provides compositions which will be important in the control of cell division and transcription.

SUMMARY OF THE INVENTION

5

The present invention is based, in part, upon the characterization of the genes and products relating to the DC-PGT, HDTEA84, HSLJD37R, RANKL, HCC5 chemokine, Dub11, Dub12, MD-1, MD-2, and cyclin E2. It provides nucleic acids, polypeptides, antibodies, and methods for making and using such compositions.

10 In the DC-PGT embodiments, the invention provides an isolated or recombinant antigenic polypeptide comprising: a plurality of distinct segments, wherein each segment has identity to at least 12 contiguous amino acids from the mature SEQ ID NO: 2; or at
15 least 17 contiguous amino acids from the mature SEQ ID NO: 2. In certain embodiments, the plurality of segments includes one of at least 19 contiguous amino acids; or two of at least 15 contiguous amino acids. Other polypeptides include those wherein the polypeptide: comprises the mature SEQ ID NO: 2; binds with
20 specificity to a polyclonal antibody which specifically binds to SEQ ID NO: 2; or the polypeptide: is a natural allelic variant of SEQ ID NO: 2; is at least 30 amino acids in length; exhibits at least two non-overlapping epitopes specific for SEQ ID NO: 2; is a synthetic polypeptide; is attached to a solid substrate; or is a
25 5-fold or less conservative substitution from SEQ ID NO: 2. Fusion polypeptides are also provided, e.g., comprising first and second portions, the first portion comprising a sequence as described and the second portion comprising a detectable marker. Pharmaceutical compositions are made available, e.g., comprising a
30 sterile polypeptide, as described, in a pharmaceutically acceptable carrier.

Polynucleotide embodiments include an isolated or recombinant polynucleotide encoding a described polypeptide. Preferred forms will be such a polynucleotide which: comprises the mature
35 polypeptide coding portion of SEQ ID NO: 1; or encodes the mature SEQ ID NO: 2. Preferred embodiments include wherein the polynucleotide is: a PCR product; a hybridization probe; a

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mutagenesis primer; or made by chemical synthesis. Alternatively, the polynucleotide is: detectably labeled; a deoxyribonucleic acid; or double stranded. Also provided is an expression vector: comprising the described polynucleotide, including wherein the polypeptide specifically binds polyclonal antibodies generated against an immunogen of mature SEQ ID NO: 2; which selectively hybridizes under stringent hybridization conditions to a target polynucleotide sequence having at least 60 contiguous nucleotides from SEQ ID NO: 1; encodes a polypeptide having at least 50 contiguous amino acid residues from mature SEQ ID NO: 2; or is suitable for transfection into a prokaryote or eukaryote host cell. Preferably, the host cell is: a mammalian cell; a bacterial cell; an insect cell; a prokaryote; a eukaryote; or a COS cell. A method is provided, e.g., of making a polypeptide comprising expressing the vector in the host cell.

Other polynucleotides include an isolated or recombinant polynucleotide which hybridizes to the coding portion of SEQ ID NO: 1 under stringent hybridization and wash conditions of at least 50° C, a salt concentration of less than 400 mM, and 50% formamide. Such a nucleic acid may be an expression vector, which may hybridize to the coding portion of SEQ ID NO: 1 under stringent hybridization and wash conditions of at least 60° C, a salt concentration of less than 200 mM, and 50% formamide. Preferably, the vector encodes a polypeptide which specifically binds an antibody generated against a mature SEQ ID NO: 2. Another embodiment will be such a polynucleotide which hybridizes to SEQ ID NO: 1, wherein the polynucleotide is: a PCR product; a hybridization probe; a mutagenesis primer; or made by chemical synthesis.

Methods are provided, e.g., of modulating the physiology or development of a cell, comprising contacting the cell with an agonist or antagonist of a described polypeptide; of detecting the presence of a complementary polynucleotide in a sample, comprising contacting a described polynucleotide that selectively hybridizes with the complementary polynucleotide in the sample to form a detectable duplex; thereby indicating the presence of the polynucleotide in the sample; or for identifying a compound that

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binds to a described polypeptide, comprising: incubating components comprising the compound and the polypeptide under conditions sufficient to allow the components to interact; and measuring the binding of the compound to the polypeptide.

5 In TNF receptor-like embodiments, the invention further provides an isolated or recombinant polynucleotide encoding an antigenic polypeptide comprising at least 17 contiguous amino acids from: the mature polypeptide from SEQ ID NO: 6; the mature polypeptide from SEQ ID NO: 8; the mature polypeptide from SEQ ID
10 NO: 10; the mature polypeptide from SEQ ID NO: 12; the mature polypeptide from SEQ ID NO: 17; the mature polypeptide from SEQ ID NO: 19; the mature polypeptide from SEQ ID NO: 21; or the mature polypeptide from SEQ ID NO: 23. In preferred embodiments, such polynucleotide will encode all of the polypeptide of: signal
15 processed SEQ ID NO: 6; signal processed SEQ ID NO: 8; signal processed SEQ ID NO: 10; signal processed SEQ ID NO: 12; signal processed SEQ ID NO: 17; SEQ ID NO: 19; SEQ ID NO: 21; or SEQ ID NO: 23. Other embodiments include such a polynucleotide, which hybridizes at 55° C, less than 500 mM salt, and 50% formamide to
20 the: mature protein coding portion of SEQ ID NO: 5; signal processed coding portion of SEQ ID NO: 7; signal processed coding portion of SEQ ID NO: 9; signal processed coding portion of SEQ ID NO: 11; mature protein coding portion of SEQ ID NO: 16; polypeptide coding portion of SEQ ID NO: 18; polypeptide coding
25 portion of SEQ ID NO: 20; or polypeptide coding portion of SEQ ID NO: 22. Other forms include those polynucleotides, comprising at least 35 contiguous nucleotides of: mature protein coding portion of SEQ ID NO: 5; signal processed coding portion of SEQ ID NO: 7; signal processed coding portion of SEQ ID NO: 9; signal processed
30 coding portion of SEQ ID NO: 11; mature protein coding portion of SEQ ID NO: 16; polypeptide coding portion of SEQ ID NO: 18; polypeptide coding portion of SEQ ID NO: 20; or polypeptide coding portion of SEQ ID NO: 22. Various expression vectors are provided comprising such a polynucleotide. The invention also provides a
35 host cell containing the expression vector, including a eukaryotic cell.

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Methods are provided, e.g., making an antigenic polypeptide comprising expressing a recombinant polynucleotide; for detecting a polynucleotide, comprising contacting the polynucleotide with a probe that hybridizes, under stringent conditions, to at least 25
5 contiguous nucleotides of the: mature protein coding portion of SEQ ID NO: 5; signal processed coding portion of SEQ ID NO: 7; signal processed coding portion of SEQ ID NO: 9; signal processed coding portion of SEQ ID NO: 11; mature protein coding portion of SEQ ID NO: 16; polypeptide coding portion of SEQ ID NO: 18;
10 polypeptide coding portion of SEQ ID NO: 20; or polypeptide coding portion of SEQ ID NO: 22; to form a duplex, wherein detection of the duplex indicates the presence of the polynucleotide. Kits are provided, e.g., for the detection of a described polynucleotide, comprising a compartment containing a probe that hybridizes, under
15 stringent hybridization conditions, to at least 17 contiguous nucleotides of a described polynucleotide to form a duplex. Preferably, the probe is detectably labeled.

Binding compounds are provided, including antibodies, comprising an antibody binding site which specifically binds to a
20 polypeptide comprising at least 17 contiguous amino acids from: signal processed SEQ ID NO: 6; signal processed SEQ ID NO: 8; signal processed SEQ ID NO: 10; signal processed SEQ ID NO: 12; signal processed SEQ ID NO: 17; SEQ ID NO: 19; SEQ ID NO: 21; or SEQ ID NO: 23. Preferably, the antibody binding site is:
25 selectively immunoreactive with the: signal processed SEQ ID NO: 6; signal processed SEQ ID NO: 8; signal processed SEQ ID NO: 10; signal processed SEQ ID NO: 12; signal processed SEQ ID NO: 17; SEQ ID NO: 19; SEQ ID NO: 21; or SEQ ID NO: 23; raised against a purified or recombinantly produced human HDTEA84 protein; raised
30 against a purified or recombinantly produced human HSLJD37R protein; or in a monoclonal antibody, Fab, or F(ab)2; or the binding compound is: an antibody molecule; a polyclonal antiserum; detectably labeled; sterile; or in a buffered composition.

Such compositions allow various methods, including using the
35 binding compound, comprising contacting the binding compound with a biological sample comprising an antigen, thereby forming a binding compound:antigen complex. Preferably, the biological

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sample is from a human, and the binding compound is an antibody. Such also allow for production of a detection kit comprising the binding compound, and: instructional material for the use of the binding compound for the detection; or a compartment providing
5 segregation of the binding compound.

Polypeptides are also made available, e.g., a substantially pure or isolated antigenic polypeptide, which binds to the described binding composition, and further comprises at least 17 contiguous amino acids from: signal processed SEQ ID NO: 6; signal
10 processed SEQ ID NO: 8; signal processed SEQ ID NO: 10; signal processed SEQ ID NO: 12; signal processed SEQ ID NO: 17; SEQ ID NO: 19; SEQ ID NO: 21; or SEQ ID NO: 23. Preferred polypeptides include those which: comprise at least a fragment of at least 25 contiguous amino acid residues from: a primate HDTEA84 protein; a
15 primate HSLJD37R protein; or a rodent or primate RANKL protein; or are soluble polypeptides; are detectably labeled; are in a sterile composition; are in a buffered composition; bind to an sialic acid residue; are recombinantly produced; or have a naturally occurring polypeptide sequence. In other embodiments, the polypeptide
20 comprises at least 17 contiguous amino acids from the: signal processed SEQ ID NO: 6; signal processed SEQ ID NO: 8; signal processed SEQ ID NO: 12; signal processed SEQ ID NO: 17; SEQ ID NO: 19; SEQ ID NO: 21; or SEQ ID NO: 23.

Methods are provided, including a method of modulating a
25 precursor cell physiology or function comprising a step of contacting the cell with: a binding compound which binds to a described polypeptide; an HDTEA84 polypeptide; an HSLJD37R polypeptide; or a RANKL polypeptide. The method may be one wherein the contacting is in combination with a TNF family ligand,
30 or an antagonist of the TNF family ligand.

In other embodiments, the present invention provides compositions related to other chemokine, Dub, or surface protein genes. Polypeptide embodiments include: a substantially pure or recombinant HCC5 polypeptide exhibiting identity over a length of
35 at least 12 amino acids to SEQ ID NO: 25; an isolated natural sequence HCC5 of mature SEQ ID NO: 25; a fusion protein comprising HCC5 sequence; a substantially pure or recombinant Dub11

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polypeptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 32 or 34; an isolated natural sequence Dub11 of mature SEQ ID NO: 32 or 34; a fusion protein comprising Dub11 sequence; a substantially pure or recombinant Dub12

5 polypeptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 36 or 38; an isolated natural sequence Dub12 of mature SEQ ID NO: 36 or 38; a fusion protein comprising Dub12 sequence; a substantially pure or recombinant MD-1

10 polypeptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 42; an isolated natural sequence MD-1 of mature SEQ ID NO: 42; a fusion protein comprising primate MD-1 sequence; a substantially pure or recombinant MD-2 polypeptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 44 or 46; an isolated natural sequence MD-2 of

15 mature SEQ ID NO: 44 or 46; a fusion protein comprising primate MD-2 sequence; a substantially pure or recombinant MD-2

20 polypeptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 48 or 49; an isolated natural sequence MD-2 of mature SEQ ID NO: 48; or a fusion protein comprising murine MD-2 sequence. Preferred embodiments include substantially pure or isolated polypeptides which match the sequences over a stretch of at least 17 amino acids; more preferably over a stretch of at least 21 amino acids; over 25, 30, 35, 50, 75 or more. In other preferred embodiments, the HCC5 polypeptide: is from a

25 primate, including a human; comprises at least one polypeptide segment of SEQ ID NO: 25; exhibits a plurality of portions exhibiting the identity; is a natural allelic variant of HCC5; has a length at least about 30 amino acids; exhibits at least two non-overlapping epitopes which are specific for a primate HCC5;

30 exhibits a sequence identity over a length of at least 35 amino acids to a HCC5; is glycosylated; is a synthetic polypeptide; is attached to a solid substrate; is conjugated to another chemical moiety; is a 5-fold or less substitution from natural sequence; or is a deletion or insertion variant from a natural sequence; or the

35 Dub11 polypeptide: is from a primate, including a human; comprises at least one polypeptide segment of SEQ ID NO: 32 or 34; exhibits a plurality of portions exhibiting the identity; is a natural

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allelic variant of Dub11; has a length at least about 30 amino acids; exhibits at least two non-overlapping epitopes which are specific for a primate Dub11; exhibits a sequence identity over a length of at least about 35 amino acids to a Dub11; is

5 glycosylated; is a synthetic polypeptide; is attached to a solid substrate; is conjugated to another chemical moiety; is a 5-fold or less substitution from natural sequence; or is a deletion or insertion variant from a natural sequence; or the Dub12

10 polypeptide: is from a primate, including a human; comprises at least one polypeptide segment of SEQ ID NO: 36 or 38; exhibits a plurality of portions exhibiting the identity; is a natural allelic variant of Dub12; has a length at least about 30 amino acids; exhibits at least two non-overlapping epitopes which are specific for a primate Dub12; exhibits a sequence identity over a

15 length of at least about 35 amino acids to a Dub12; is glycosylated; is a synthetic polypeptide; is attached to a solid substrate; is conjugated to another chemical moiety; is a 5-fold or less substitution from natural sequence; or is a deletion or insertion variant from a natural sequence; or the primate MD-1

20 polypeptide: is from a human; comprises at least one polypeptide segment of SEQ ID NO: 42; exhibits a plurality of portions exhibiting the identity; is a natural allelic variant of primate MD-1; has a length at least about 30 amino acids; exhibits at least two non-overlapping epitopes which are specific for a

25 primate MD-1; exhibits a sequence identity over a length of at least about 35 amino acids to a primate MD-1; is glycosylated; is a synthetic polypeptide; is attached to a solid substrate; is conjugated to another chemical moiety; is a 5-fold or less substitution from natural sequence; or is a deletion or insertion

30 variant from a natural sequence; or the primate MD-2 polypeptide: is from a human; comprises at least one polypeptide segment of SEQ ID NO: 44 or 46; exhibits a plurality of portions exhibiting the identity; is a natural allelic variant of primate MD-2; has a length at least about 30 amino acids; exhibits at least two non-

35 overlapping epitopes which are specific for a primate MD-2; exhibits a sequence identity over a length of at least about 35 amino acids to a primate MD-2; is glycosylated; is a synthetic

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polypeptide; is attached to a solid substrate; is conjugated to another chemical moiety; is a 5-fold or less substitution from natural sequence; or is a deletion or insertion variant from a natural sequence; or the rodent MD-2 polypeptide: is from a mouse; comprises at least one polypeptide segment of SEQ ID NO: 48 or 49; exhibits a plurality of portions exhibiting the identity; is a natural allelic variant of rodent MD-2; has a length at least about 30 amino acids; exhibits at least two non-overlapping epitopes which are specific for a rodent MD-2; exhibits a sequence identity over a length of at least about 35 amino acids to a rodent MD-2; is glycosylated; is a synthetic polypeptide; is attached to a solid substrate; is conjugated to another chemical moiety; is a 5-fold or less substitution from natural sequence; or is a deletion or insertion variant from a natural sequence.

Sterile compositions comprising such polypeptides are also provided, along with those comprising: the HCC5 polypeptide and: a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration; another chemokine, including one selected from the group of HCC1, HCC2, HCC3, and HCC4; or an antibody antagonist for a chemokine, including one selected from the group of HCC1, HCC2, HCC3, and HCC4; the Dub11 polypeptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration; the Dub12 polypeptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration; the MD-1 polypeptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration; the MD-2 polypeptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration.

Fusion proteins are provided, e.g., comprising: mature protein sequence of SEQ ID NO: 25; mature protein sequence of SEQ

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ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36 or SEQ ID NO: 38; mature protein sequence of SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, or SEQ ID NO: 49; a detection or purification tag, including a FLAG, His6, or Ig sequence; or sequence of another chemokine protein with the chemokine polypeptide Kits are provided, e.g., comprising a described polypeptide and: a compartment comprising the polypeptide; and/or instructions for use or disposal of reagents in the kit.

Binding compounds, including antibodies, are provided, e.g., comprising an antigen binding portion from an antibody, which specifically binds to a natural: HCC5 polypeptide, wherein the antibody: is raised against a peptide sequence of a mature HCC5 polypeptide sequence of SEQ ID NO: 25; is raised against a mature HCC5; is raised to a purified HCC5; is immunoselected; is a polyclonal antibody; binds to a denatured HCC5; or exhibits a Kd to HCC5 antigen of at least 30 μ M; or Dub11 polypeptide, wherein the antibody: is raised against a peptide sequence of a mature Dub11 polypeptide sequence of SEQ ID NO: 32 or SEQ ID NO: 34; is raised against a mature Dub11; is raised to a purified Dub11; is immunoselected; is a polyclonal antibody; binds to a denatured Dub11; or exhibits a Kd to Dub11 antigen of at least 30 μ M; or Dub12 polypeptide, wherein the antibody: is raised against a peptide sequence of a mature Dub12 polypeptide sequence of SEQ ID NO: 36 or SEQ ID NO: 38; is raised against a mature Dub12; is raised to a purified Dub12; is immunoselected; is a polyclonal antibody; binds to a denatured Dub12; or exhibits a Kd to Dub12 antigen of at least 30 μ M; or a primate MD-1 polypeptide, wherein the antibody: is raised against a peptide sequence of a mature polypeptide sequence of SEQ ID NO: 42; is raised against a mature MD-1; is raised to a purified MD-1; is immunoselected; is a polyclonal antibody; binds to a denatured MD-1; or exhibits a Kd to MD-1 antigen of at least 30 μ M; or a primate MD-2 polypeptide, wherein the antibody: is raised against a peptide sequence of a mature MD-2 polypeptide sequence of SEQ ID NO: 44, or SEQ ID NO: 46; is raised against a mature MD-2; is raised to a purified MD-2; is immunoselected; is a polyclonal antibody; binds to a denatured

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MD-2; or exhibits a Kd to MD-2 antigen of at least 30 μ M; or a rodent MD-2 polypeptide, wherein the antibody: is raised against a peptide sequence of a mature MD-2 polypeptide sequence of SEQ ID NO: 48, or SEQ ID NO: 49; is raised against a mature rodent MD-2; is raised to a purified rodent MD-2; is immunoselected; is a polyclonal antibody; binds to a denatured rodent MD-2; or exhibits a Kd to antigen of at least 30 μ M. In certain embodiments, the binding composition will be one wherein: the polypeptide is from a primate or rodent; the binding compound is an Fv, Fab, or Fab2 fragment; the binding compound is conjugated to another chemical moiety; is attached to a solid substrate, including a bead or plastic membrane; is in a sterile composition; or is detectably labeled, including a radioactive or fluorescent label.

Kits are provided comprising the binding compound, and: a compartment comprising the binding compound; a compartment comprising purified antigen; and/or instructions for use or disposal of reagents in the kit. Methods are provided for producing an antigen:antibody complex, comprising contacting an antibody and: a primate HCC5 polypeptide; a primate Dub11 polypeptide; a primate Dub12 polypeptide; a primate MD-1 polypeptide; a primate MD-2 polypeptide; or a rodent MD-2 polypeptide; thereby allowing the complex to form. Other compositions are provided, e.g., the binding compound and: a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration; or an antibody antagonist for another chemokine, including one selected from the group of HCC1, HCC2, HCC3, and HCC4.

Nucleic acid embodiments include, e.g., an isolated or recombinant nucleic acid encoding a polypeptide or fusion protein described, wherein: the HCC5: polypeptide is from a primate, including a human; or nucleic acid: encodes an antigenic HCC5 peptide sequence of SEQ ID NO: 25 encodes a plurality of antigenic HCC5 peptide sequences of SEQ ID NO: 25; exhibits identity over at least 25 nucleotides to a natural cDNA encoding the HCC5 segment; is a hybridization probe for a gene encoding the HCC5 polypeptide;

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or further encodes another chemokine, including one selected from the group of HCC1, HCC2, HCC3, and HCC4; or the Dub11: polypeptide is from a primate, including a human; or nucleic acid: encodes a Dub11 antigenic peptide sequence of SEQ ID NO: 32; or SEQ ID NO: 34; encodes a plurality of antigenic peptide sequences of SEQ ID NO: 32 or SEQ ID NO: 34; exhibits identity over at least 25 nucleotides to a natural cDNA encoding the Dub11 segment; or is a hybridization probe for a gene encoding the Dub11 polypeptide; the Dub12: polypeptide is from a primate, including a human; or nucleic acid: encodes an antigenic Dub12 peptide sequence of SEQ ID NO: 36 or SEQ ID NO: 38; encodes a plurality of antigenic peptide sequences of SEQ ID NO: 36 or SEQ ID NO: 38; exhibits identity over at least 25 nucleotides to a natural cDNA encoding the DUB12 segment; is a hybridization probe for a gene encoding the Dub12 polypeptide; or the primate MD-1: polypeptide is from a primate, including a human; or nucleic acid: encodes an antigenic MD-1 peptide sequence of SEQ ID NO: 42; encodes a plurality of antigenic peptide sequences of SEQ ID NO: 42; exhibits identity over at least 25 nucleotides to a natural cDNA encoding the MD-1 segment; is a hybridization probe for a gene encoding the Dub11 polypeptide; or the primate MD-2: polypeptide is from a human; or nucleic acid: encodes an antigenic MD-2 peptide sequence of SEQ ID NO: 44, or SEQ ID NO: 46; encodes a plurality of antigenic peptide sequences of SEQ ID NO: 44, or SEQ ID NO: 46; exhibits identity over at least 25 nucleotides to a natural cDNA encoding the segment; is a hybridization probe for a gene encoding the primate MD-2 polypeptide; or the rodent MD-2: polypeptide is from a mouse; or nucleic acid: encodes an antigenic MD-2 peptide sequence of SEQ ID NO: 48, or SEQ ID NO: 49; encodes a plurality of antigenic peptide sequences of SEQ ID NO: 48, or SEQ ID NO: 49; exhibits identity over at least 25 nucleotides to a natural cDNA encoding the MD-2 segment; or is a hybridization probe for a gene encoding the rodent MD-2 polypeptide. Other nucleic acid embodiments include the described, which: is an expression vector; further comprises an origin of replication; is from a natural source; comprises a detectable label; comprises synthetic nucleotide sequence is less than 6 kb, preferably less than 3 kb; is from a

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primate, including a human; comprises a natural full length coding sequence; or is a PCR primer, PCR product, or mutagenesis primer.

Various cells are provided, including a cell or tissue comprising a described recombinant nucleic acid, including wherein
5 the cell is: a prokaryotic cell; a eukaryotic cell; a bacterial cell; a yeast cell; an insect cell; a mammalian cell; a mouse cell; a primate cell; or a human cell.

Kits are provided, e.g., comprising a described nucleic acid, and: a compartment comprising the nucleic acid; a compartment
10 comprising a nucleic acid encoding another chemokine, including HCC1, HCC2, HCC3, and HCC4; or instructions for use or disposal of reagents in the kit.

Alternative nucleic acids include those which: hybridize under wash conditions of 45° C and less than 2M salt to the
15 polypeptide coding portion of SEQ ID NO: 24; hybridize under wash conditions of 45° C and less than 2M salt to the polypeptide coding portions of SEQ ID NO: 31 or 33; hybridize under wash conditions of 45° C and less than 2M salt to the coding portions of SEQ ID NO: 35 or 37; hybridize under wash conditions of 45° C
20 and less than 2M salt to the coding portion of SEQ ID NO: 41; hybridize under wash conditions of 45° C and less than 2M salt to the coding portion of SEQ ID NO: 43 or 45. or hybridize under wash conditions of 45° C and less than 2M salt to the coding portion of SEQ ID NO: 47. Preferably, the wash conditions are at 55° C
25 and/or 500 mM salt; or at 65° C and/or 150 mM salt.

Additionally, methods are provided, e.g., of modulating physiology or development of a cell or tissue culture cells comprising exposing the cell to an agonist or antagonist of HCC5, primate MD-1, primate MD-2, or rodent MD-2. Others include
30 methods of detecting specific binding to a compound, comprising: contacting the compound to a composition selected from the group of: an antigen binding site which specifically binds to: an HCC5 chemokine; a Dub11; a Dub12; a primate MD-1; a primate MD-2; a rodent MD-2; or an expression vector encoding: an HCC5 chemokine
35 or fragment thereof; a Dub11 or fragment thereof; a Dub12 or fragment thereof; a primate MD-1 or fragment thereof; a primate MD-2 or fragment thereof; or a rodent MD-2 or fragment thereof; a

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substantially pure protein which is specifically recognized by the antigen binding site of the described antigen binding sites; a substantially pure HCC5 chemokine or peptide thereof, or a fusion protein comprising a 30 amino acid sequence portion of HCC5
5 chemokine sequence; a substantially pure Dub11 or peptide thereof, or a fusion protein comprising a 30 amino acid sequence portion of Dub11 sequence; a substantially pure Dub12 or peptide thereof, or a fusion protein comprising a 30 amino acid sequence portion of Dub11 sequence; a substantially pure primate MD-1 or peptide
10 thereof, or a fusion protein comprising a 30 amino acid sequence portion of primate MD-1 sequence; a substantially pure primate MD-2 or peptide thereof, or a fusion protein comprising a 30 amino acid sequence portion of primate MD-2 sequence; a substantially pure rodent MD-2 or peptide thereof, or a fusion protein
15 comprising a 30 amino acid sequence portion of rodent MD-2 sequence; and then detecting binding of the compound to the composition.

Particular polynucleotide embodiments include an isolated or recombinant polynucleotide which: encodes at least 17 contiguous
20 amino acid residues of SEQ ID NO: 54; encodes at least two distinct segments of at least 10 contiguous amino acid residues of SEQ ID NO 54; or comprises one or more segments at least 21 contiguous nucleotides of SEQ ID NO: 53. Such polynucleotides allow methods of making: a polypeptide comprising expressing a
25 described expression vector, thereby producing the polypeptide; a duplex nucleic acid comprising contacting a polynucleotide with a complementary nucleic acid, thereby resulting in production of the duplex nucleic acid; a synthetic polynucleotide, comprising chemically polymerizing nucleotides to produce the polynucleotide;
30 or a polynucleotide comprising using a PCR method.

Cyclin polypeptide embodiments include an isolated or recombinant antigenic polypeptide comprising at least: one segment comprising at least 17 contiguous amino acids from SEQ ID NO: 54;
35 or at least two distinct segments of at least 11 contiguous amino acids from SEQ ID NO: 54. Such polypeptide may: comprise at least one segment comprising at least 17 contiguous amino acids from SEQ ID NO: 54; and exhibit at least two non-overlapping epitopes which

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are selective for primate protein of SEQ ID NO: 54. Other embodiments include those wherein the polypeptide: is a 5-fold or less substitution from a natural sequence; is a deletion or insertion variant from a natural sequence; or comprises at least two distinct segments of at least 11 contiguous amino acids from SEQ ID NO: 54. Preferably the polypeptide is antigenic, and will typically comprise at least one sequence from (SEQ ID NO: 54) KESRYVHD (residues 120-127), DKHFEVLH (residues 127-134), HSDLEPQM (residues 134-141), QKDINKNM (residues 177-184), YAPKLQEF (residues 203-210), SEEDILRM (residues 219-226), LRMELIIL (residues 224-231), ELCPVTII (residues 237-244), and LFLQVDAL (residues 249-256); and/or the segments of at least 11 contiguous amino acids comprise one the segment with at least 14 contiguous amino acids from SEQ ID NO: 54. Such polypeptides may further exhibit at least two non-overlapping epitopes which are selective for primate protein of SEQ ID NO: 54; and/or may: comprise a mature sequence of SEQ ID NO: 2; bind with selectivity to an antibody generated against an immunogen of SEQ ID NO: 54; comprise a plurality of polypeptide segments of 17 contiguous amino acids of SEQ ID NO: 54; or be a natural allelic variant of SEQ ID NO: 54. The polypeptide may: be in a sterile composition; have a length at least 30 amino acids; be not glycosylated; be denatured; be a synthetic polypeptide; be attached to a solid substrate; or be a fusion protein with a detection or purification tag, including a FLAG, His6, or Ig sequence. Other embodiments include those wherein the polypeptide: is a 5-fold or less substitution from a natural sequence; or is a deletion or insertion variant from a natural sequence.

Various kits are provided, e.g., which comprise such polypeptides and instructions for the use or disposal of the polypeptide or other reagents of the kit.

Methods are provided, e.g., to label the polypeptide, comprising labeling the polypeptide with a radioactive label; to separate the polypeptide from another polypeptide in a mixture, comprising running the mixture on a chromatography matrix, thereby separating the polypeptides; to identify a compound that binds selectively to the polypeptide, comprising incubating the compound

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with the polypeptide under appropriate conditions; thereby causing the component to bind to the polypeptide; to conjugate the polypeptide to a matrix, comprising derivatizing the polypeptide with a reactive reagent, and conjugating the polypeptide to the matrix; or inducing an antibody response to the polypeptide, comprising introducing the polypeptide as an antigen to an immune system, thereby inducing the response.

Binding compounds are provided, e.g., antibodies, comprising an antigen binding portion from an antibody which binds with selectivity to described polypeptides. Methods are made available for evaluating the selectivity of binding of a compound to cyclin E2, comprising contacting the compound to a recombinant cyclin E2 polypeptide and at least one other cyclin; and comparing binding of the compound to the cyclins.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

5 All references cited herein are incorporated herein by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

I. General

10 It is to be understood that this invention is not limited to the particular compositions, methods, and techniques described herein, as such compositions, methods, and techniques may vary. It is to be understood that the terminology used herein is for the purpose of describing particular embodiments, and is not intended to limit the scope of the present invention which is to be limited
15 by the appended claims.

As used herein, including the appended claims, singular forms of words such as "a," "an," and "the" include their corresponding plural referents unless the context clearly dictates otherwise. Thus, e.g., reference to "a polynucleotide" includes one or more
20 different polynucleotides, reference to "a composition" includes one or more of such compositions, and reference to "a method" includes reference to equivalent steps and methods known to a person of ordinary skill in the art, and so forth.

25 Unless otherwise defined, technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described
30 below. All publications, patent applications, patents, and other references discussed above are provided for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the invention is not entitled to antedate any such disclosure by virtue of its prior invention.

35 The present invention also provides amino acid sequences and DNA sequences encoding various mammalian proteins, e.g., which are polypeptides produced by selected cells. Among these proteins are

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those which: mediate uptake of substrates, e.g., prostaglandin-like molecules, modulate or mediate, e.g., induce or prevent trafficking, proliferation, or differentiation of, interacting cells, or are intracellular proteins which are important in various cellular processes, e.g., deubiquitination of proteins or cell cycle regulation.

The Prostaglandin-like Transporter (PGT) of the present invention is expressed particularly in antigen presenting cells of the immune system, e.g., dendritic cells. As such, the transporter is designated a dendritic cell prostaglandin-like transporter (DC-PGT). Consequently, the DC-PGT of the present invention offers the means to establish fundamental understanding on the role of PG influence on immune function.

The present invention provides DNA sequence encoding a mammalian protein that exhibits structural features characteristic of functionally significant proteins, particularly which serve as organic anion transporters. This family of organic anion transporters includes: the prostaglandin transporters of man (Lu, et al. (1996) J. Clin. Invest. 98:1142-1149) and rat; organic anion transporters in man and rat; brain digoxin transporters and Matrin F/G of rat (Kanai, et al. (1995) Science 268:866-869).

Transporters of this family typically are 12 transmembrane proteins of approximately 650 amino acids in length. Characteristic of this group of proteins is a cysteine rich region located in one of the extracellular loops, which resembles a zinc finger motif. It is not entirely certain whether these polypeptides mediate primarily the influx or efflux of prostaglandins and organic anions, and they may, under different circumstances produce influx or efflux depending, e.g., on the intracellular concentration of the organic anions concerned.

The DC PGT protein of the present invention is closest in homology to the prostaglandin transporters and it is probable that a prostaglandin is the major anion transported. The human gene embodiment described herein, isolated as designate DC-PGT or clone 240, contains an open reading frame encoding a presumptive protein of about 709 amino acids. This protein exhibits intracellular, transmembrane, and extracellular protein segments, revealing novel

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aspects of organic anion transport that may be relevant during mammalian development, e.g., development of dendritic cells of the immune system.

The introduction of evolutionary information in the form of sequence homologs simplifies the structural analysis considerably for related molecules which share a common structural framework in spite of considerable sequence divergence, see, e.g., Chothia and Lesk (1986) EMBO J. 5:823-826. This concept can be effectively extended to the strong prediction of TM regions across an aligned protein family, whereas any single sequence may provide an uncertain topology. See Persson and Argos (1994) J. Mol. Biol. 237:182-192; and Rost, et al. (1995) Protein Sci. 4:521-533. For the DC PGT, a number of sequence homologs were first assembled by comparative matching to protein and translated nucleotide databases (Altschul, et al. (1994) Nature Genet. 6:119-129; Koonin, et al. (1994) EMBO J. 13:493-503). These relatives of DC-PGT include a ubiquitously expressed PGT from primate, e.g., human (GenBank: locus HSU70867, accession U70867), and a PGT from rodent, e.g., rat (prostaglandin transporter - rat, GenBank Acc. No. 1083766; Kanai, et al. (1995) Science 268:866-869). These sequences were subjected to parallel analyses by a suite of computer programs that have greatly improved on the initial Kyte and Doolittle (1982) hydropathic profile as a means of predicting the topology of integral membrane proteins. Four algorithms (ALOM, MTOP, MEMSAT and TopPredII) (Klein, et al. (1985) Biochim. Biophys. Acta 815:468-476; Hartmann, et al. (1989) Proc. Nat'l Acad. Sci. USA 86:5786-5790; Jones, et al. (1994) Biochem. Biophys. Res. Commun. 202:33-39; and Claros and von Heijne (1994) Comp. Applic. Biosci. 10:685-686) were used to individually predict TM extensions and orientations; these predictions were pooled and mapped onto the multiple sequence alignment produced by ClustalW and MACAW (Thompson, et al. (1994) Nucl. Acids Res. 22:4673-4680; and Schuler, et al. (1991) Proteins 9:180-190). Furthermore, these multiply aligned sequence files were used as input to PHD and TMAP (Rost, et al. (1995) Protein Sci. 4:521-533; Persson and Argos (1994) J. Mol. Biol. 237:182-192) for a familial prediction

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of shared TM regions. Structural features that persisted in this two-step analysis are likely to be shared topological traits present in all members of this organic anion transporter family.

HDTEA84, HSLJD37R, and RANKL genes and proteins are also provided, which are related to the TNF signaling pathways. The antigens HDTEA84, HSLJD37R, and RANKL, and fragments, or antagonists will be useful in physiological modulation of cells expressing receptors for, e.g., ligands of the TNF family. Some of these antigens appear to lack a membrane spanning segment, suggesting that they are soluble forms of receptor. This suggests that the soluble proteins can serve as antagonists of the TNF-like ligands. In addition, it is likely that membrane spanning forms exist, which serve as signaling receptors mediating cellular response to the ligands.

The HDTEA84 gene has been detected in cDNA libraries derived from Hodgkin's lymphoma, endothelial cells, keratinocytes, prostate, and cerebellum. It exhibits significant sequence similarity to the osteoprotegerin ligand receptor reported by Lacey, et al. (1998) Cell 93:165-176. The HDTEA84 will likely modulate proliferation or development by antagonizing its respective ligand. Membrane associated forms should exist, likely alternatively spliced transcription products.

The HSLJD37R exhibits like similarity to receptors for TNF. While the first embodiment is an incomplete sequence, the available portion currently lacks an identified transmembrane segment. Additional efforts provide a full length sequence, and an alternative splice variant.

The rodent 427152#4 Rank-like (RANKL) was detected in a rodent cDNA library panel probed with Mouse 427152#4 (204 bp). Positive signals were detected in CH12 (B cell line); rag-1 thymus; rag-1 heart; rag-1 brain (best signal); rag-1 testes; rag-1 liver; normal lung; rag-1 lung; asthmatic lung; tolerized and challenged lung; Nippo-infected lung; Nippo IL-4 K.O. lung; Nippo anti-IL-5 treated lung; influenza lung; guinea pig allergic lung; w.t. stomach; and w.t. colon on a 3 day exposure at -80° C with an intensifier screen. On a 2 week exposure at -80° C with screen, signals were also detected in the following libraries: Mell14+

naive; Mel14+ Th1; Mel14+ Th2; Th1 3 week B1/6; large B cell;
bEnd3 + TNF α + IL-10, guinea pig normal lung; and Rag Hh- colon.

The primate, e.g., human, Rank-like (RANKL) homologs of
rodent 427152#4 were detected in a human cDNA library panel probed
5 with mouse 427152#4 (204 bp). Signals were detected in monkey
asthma lung 4 h (1.6-2.0 kb) and adult placenta (2.5-3.0 kb) on a
3 day exposure at -80° C with screen. On a 2 week exposure at -
80° C with screen, signals were also detected in the following
libraries: CD1a+ 95% DC activated CHA (kidney epithelial carcinoma
10 cell line); monkey lung normal; psoriasis skin; fetal lung; fetal
ovary; fetal testes; and fetal spleen.

Each of these proteins will also be useful as antigens, e.g.,
immunogens, for raising antibodies to various epitopes on the
protein, linear and/or conformational epitopes. The molecules may
15 be useful in defining various cell subsets, either by the
molecules produced by, or by expression of membrane forms of the
receptors. Such cells should be responsive to the respective
ligands. Soluble forms of the receptors should serve as
antagonists of the ligand, binding to the ligand and preventing
20 interaction with membrane forms, which would mediate signaling.

Both genes express proteins which exhibit structural motifs
characteristic of a member of the TNF receptor family. SEQ ID NO: 5
and SEQ ID NO: 6, respectively, provide the nucleic acid and
predicted amino acid sequences for primate, e.g., human, HDTEA84.
25 SEQ ID NO: 7 and SEQ ID NO: 8, respectively, provide the nucleic
acid and predicted amino acid sequences for primate, e.g., human,
HSLJD37R.

Interesting features of the HDTEA84 include: signal sequence
from about 1-11; TNF receptor Cys rich domains I (about 32-72), II
30 (about 73-113), III (about 114-150), and IV (about 151-193); and
unique region from about 194-300. Features for the HSLJD37R (SEQ
ID NO: 10 form), partly based on alignment with HDTEA84: signal
sequence from about 1-41; TNF receptor Cys rich domains I (about
42-90), II (about 91-131), III (about 132-168), and IV (about 169-
35 211); transmembrane segment from about 354-370. Similar alignment
of the other variants will identify similar features. Segments
including combinations or excluding such segments may be desired.

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The structural homology of HDTEA84, HSLJD37R, and RANKL to members of the TNF receptor family suggests related function of these molecules. See, e.g., Lacey, et al. (1998) Cell 93:165-176. The sequences, however, mostly lack a transmembrane segment, suggesting that the proteins are soluble receptor forms. They may well also have membrane bound forms resulting, e.g., from alternatively spliced transcript variants. The soluble forms are likely to be antagonists of the ligand, e.g., blocking the binding of ligand to a membrane bound form of signaling receptor. Thus, these molecules may be useful in the treatment of abnormal immune or developmental disorders.

The natural antigens should be capable of modulating various biochemical responses which lead to biological or physiological responses in target cells. The embodiments characterized herein are from primate, e.g., human, but other species variants almost surely exist, e.g., rodents, etc. See below. The descriptions below are directed, for exemplary purposes, to primate HDTEA84, HSLJD37R, or RANKL, but are likewise applicable to related embodiments from other species.

The HDTEA84, HSLJD37R, and RANKL clones were assembled through the careful analysis of ESTs present in various databases, e.g., Merck-WashU public database. These genes exhibit structural motifs characteristic of a member of the TNF receptor family. Compare, e.g., with the TNF receptor, NGF-receptor, and FAS receptor. Table 3 discloses the nucleic acid and predicted amino acid sequences for primate, e.g., human, HDTEA84. The ESTs were identified from several different libraries.

SEQ ID NO: 7 AND SEQ ID NO: 8, respectively, disclose partial nucleic acid and predicted amino acid sequences for primate, e.g., human, HSLJD37R. The ESTs were identified from several different libraries derived from: smooth muscle, pancreas tumor, adipocytes, HUVEC cells, adult pulmonary, endothelial cells, prostate cell line PC3, microvascular endothelial cells, fetal heart, and dendritic cells. Other sequences were detected in libraries from: multiple sclerosis lesions, breast, kidney, and germinal center B cells.

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SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20 and SEQ ID NO: 22 provide the sequences of various mammalian genes designated RANKL.

Interesting features of the rodent RANKL include: signal sequence from about 1-29; TNF receptor Cys rich domain I (about 33-74), II (about 75-114), and III (about 115-135). Interesting features of the primate RANKL include: TNF receptor Cys rich domain I (about 1-43), II (about 44-83), and III (about 84-104); transmembrane segment from about 139-155. Alignment with other TNF receptors will identify additional interesting corresponding features. Segments with boundaries at these positions may be especially interesting.

Hybridization signals with RANKL were detected with rodent, e.g., mouse sequence, in CH12 (B cell line), rag-1 thymus, rag-1 heart, rag-1 brain (strongest signal), rag-1 testes, rag-1 liver, normal lung, rag-1 lung, asthmatic lung, tolerized and challenged lung, Nippo-infected lung, Nippo IL-4 K.O. lung, Nippo anti-IL-5 lung, influenza lung, guinea pig allergic lung, w.t. stomach, and w.t. colon on a 3 day exposure at -80° C with a screen. On a 2 week exposure at -80° C with screen, signals were also detected in the following libraries: Mel 14+ naive, Mel14+ Th1, Mel14+ Th2, Th1 3 week B1/6, large B cell, bEnd3 + TNF α + IL-10, guinea pig normal lung, and Rag Hh- colon. Probes of human libraries with rodent sequence provided: detectable signals in Monkey asthma lung 4 h (1.6-2.0 kb) and adult placenta (2.5-3.0 kb) on a 3 day exposure at -80° C with screen. On a 2 week exposure at -80° C with screen, signals were also detected in the following libraries: CD1a+ 95% DC activated, CHA (kidney epithelial carcinoma cell line), monkey lung normal, psoriasis skin, fetal lung, fetal ovary, fetal testes, and fetal spleen.

In another embodiment, the invention provides a chemokine. For a review of the chemokine family, see, e.g., Lodi, et al. (1994) Science 263:1762-1767; Gronenborn and Clore (1991) Protein Engineering 4:263-269; Miller and Kranger (1992) Proc. Nat'l Acad. Sci. USA 89:2950-2954; Matsushima and Oppenheim (1989) Cytokine 1:2-13; Stoeckle and Baker (1990) New Biol. 2:313-323; Oppenheim, et al. (1991) Ann. Rev. Immunol. 9:617-648; Schall (1991) Cytokine

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3:165-183; and Thomson (ed. 1994) The Cytokine Handbook 2d ed. Academic Press, NY.

The new chemokine described herein is designated HCC5 which is a CC chemokine. See SEQ ID NO: 24 and SEQ ID NO: 25. The descriptions are directed, for exemplary purposes, to the human HCC5 natural allele described, but are likewise applicable to allelic and/or polymorphic variants, e.g., from other individuals, as well as splicing variants, e.g., natural forms. Based on sequence analysis of the chemokine protein sequences described below, it is apparent that HCC5 belongs to the CC chemokine family. See, e.g., stem cell mobilizing chemokine (CKbeta-1) from Kreider, et al. (1997) Patent WO 9715594 (SEQ ID NO: 26) and GenBank Accession number 97P-W17659; macrophage inflammatory protein-1-gamma (MIP-1) from Adams, et al. (1995) Patent WO 9517092 (SEQ ID NO: 27) and GenBank Accession number 95P-R76128; human MIP-4, a chemoattractant for leukocytes from Adams, et al. (1997) Patent WO 9634891 (SEQ ID NO: 28) and GenBank Accession number 96P-W07203; pituitary expressed chemokine (PGEC) from Bandman, et al., Patent WO 9616979 (SEQ ID NO: 29) and GenBank Accession number 96P-R95691; and human chemokine HCC-1 from Forsmann, et al. (1998) Patent WO 9741230 (SEQ ID NO: 30) and GenBank Accession number 97P-W38171.

The HCC5 chemokine was discovered through searches and careful analysis of database sequences. The HCC5 sequence was discovered in a cDNA library from pooled bulk breast tumor tissue. Absence of overlapping sequences from other sources suggests extremely specific tissue expression, or highly regulated expression. Amino acid homology analysis suggests that the HCC5 gene encodes a member of a group of related family of chemokines. The primate, e.g., human, HCC5 chemokine is most closely related in sequence to the chemokines, human chemokine HCC1; human pituitary expressed chemokine (PGEC); human MIP-4 (a chemoattractant for leukocytes); human macrophage inflammatory protein-1-gamma (MIP-1γ); and human stem cell mobilizing chemokine (CKbeta-1).

The HCC5 chemokine is seemingly specifically expressed, since its sequence has not appeared from many sources. The structural

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similarity to other chemokines suggests that signals important in inflammation, cell differentiation, and development are mediated by it.

It is possible that the HCC5 may actually be an antagonist of one, some, or all, of many related chemokines. In such case, combination compositions may be desired. For example, a combined group of functional agonists and antagonists for specific receptors may be called for, e.g., a combination of chemokines and antibody antagonists of others. In addition, HCC5 may be useful to block HIV or HTLV infection, which viruses may use the respective receptors for infection.

The HCC5 chemokine exhibits limited similarity to portions of known chemokines. See, e.g., Matsushima and Oppenheim (1989) Cytokine 1:2-13; Oppenheim, et al. (1991) Ann. Rev. Immunol. 9:617-648; Schall (1991) Cytokine 3:165-183; and Gronenborn and Clore (1991) Protein Engineering 4:263-269. Other features of comparison are apparent between the HCC5 chemokine and chemokine families. See, e.g., Lodi, et al. (1994) Science 263:1762-1766. In particular, β -sheet and α -helix residues can be determined using, e.g., RASMOL program, see Sayle and Milner-White (1995) TIBS 20:374-376; or Gronenberg, et al. (1991) Protein Engineering 4:263-269; and other structural features are defined in Lodi, et al. (1994) Science 263:1762-1767. These secondary and tertiary features assist in defining further the C, CC, CXC, and CX3C structural features, along with spacing of appropriate cysteine residues.

Antagonists might be created by N-terminal modification, e.g., either truncation or addition of an N-terminal methionine. Since HCC5 is structurally related to the HCC chemokines, it may well exhibit similar behaviors and functions.

The distribution of the HCC5 chemokines, especially in dendritic cells, or in Th1 T cells, B cells, and macrophages, suggest roles in immune functions, e.g., it will likely attract T cells and monocytes. Thus, the HCC5 chemokine is likely to recruit these cell types in vivo, thereby enhancing the immune response mediated by these cell types. The expression patterns

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appear consistent with a functional importance of the ligands in a TH1/TH2 regulation and/or response, including, e.g., in a cancer therapy. Thus, ligands and homologs are identified as possible immune adjuvants, e.g., for cellular responses, but also as possible adjuvants to modulate soluble antigen responses, e.g., vaccines.

The invention further provides mammalian, e.g., primate, DNA sequences encoding proteins which exhibit structural properties of likely intracellular deubiquitinating protein enzymes. These proteins are designated deubiquitinating 11 (Dub11) and deubiquitinating 12 (Dub12). For a review of the superfamily of deubiquitinating enzymes see, e.g., Hochstrasser (1995) Curr. Opin. Cell Biol. 7:215-223; Wilkinson, et al. (1995) Biochemistry 34:14535-14546; Baker, et al. (1992) J. Biol. Chem. 267:23364-23375; and Papa and Hochstrasser (1993) Nature 366:313-319. However, the deubiquitinating enzymes have also been reported to have additional functions besides deubiquitination. See, e.g., Hochstrasser (1996) Cell 84:813-815; Hicke and Riezman (1996) Cell 84:277-287; and Chen, et al. (1996) Cell 84:853-862.

The descriptions typically are directed, for exemplary purposes, to the human Dub11 and human Dub12 natural alleles described, but are likewise applicable to allelic and/or polymorphic variants, e.g., from other individuals, as well as splicing variants, e.g., natural forms, and species variants from other primates or other species. These genes will allow isolation of other primate genes encoding proteins related to this, further extending the family beyond the specific embodiments described.

The Dub11 or Dub12 proteins (naturally occurring or recombinant), fragments thereof, and antibodies thereto, along with compounds identified as having binding affinity to Dub11 or Dub12, may be useful in the treatment of conditions associated with abnormal physiology or development, such as, e.g., uterine carcinoma associated with p53 dysregulation associated with human papilloma virus or mental retardation of Angelman syndrome (AS) due to disruption of the 5' end of the UBE3A (E6-AP) gene which codes for a disubiquitination protein. Pharmacological intervention which alters the half-lives of cellular proteins

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associated with these diseases may have wide therapeutic potential. Specifically, prevention of p53 ubiquitination (and subsequent degradation) in human papilloma virus positive tumors, and perhaps all tumors retaining wild-type p53 but lacking the retinoblastoma gene function, could lead to programmed cell death. Additionally, specific inhibitors of p27 and cyclin B ubiquitination are predicted to be potent antiproliferative agents. Inhibitors of IkappaB ubiquitination should prevent NFkappaB activation and may have utility in a variety of autoimmune and inflammatory conditions. Finally, deubiquitination enzymes may be novel, potential drug targets as they also appear to regulate cell proliferation. These conditions or disease states may be modulated by appropriate therapeutic treatment using the deubiquitination compositions provided herein.

Conversely, methods for blocking the enzymatic activities should have the opposite effects. Small molecule drug screening to block enzymatic activity of the protein can be performed to identify entities which will block the deubiquitination, thereby affecting protein degradation pathways, as appropriate.

The T cell growth factor interleukin-2 (IL-2) regulates lymphocyte proliferation by inducing the expression of growth promoting genes. HTLV-1 transformed cell lines derived from Adult T-cell Leukemia (ATL) can exhibit constitutive activation of the IL-2-induced JAK/STAT pathway. See Migone, et al. (1998) Proc. Nat'l Acad. Sci. USA 95:3845-3850. ATL cell lines were examined for expression of IL-2 induced genes. It was found that the deubiquitinating enzyme Dub2 is constitutively expressed. See Zhu, et al. (1997) J. Biol. Chem. 272:51-57. Moreover, Dub2 expression conferred cytokine-independent proliferation on the interleukin-3-dependent murine Ba/F3 hematopoietic cell line. SCID mice (n = 18) subcutaneously injected with Ba/F3 cells expressing Dub2, (but not a C to S inactive mutant of Dub2) developed tumors with a six week latency. Cells derived from these tumors exhibited constitutive tyrosine phosphorylation of STAT5 and also mimicked the ATL cell lines by exhibiting down-regulation of the protein tyrosine phosphatase SHP-1. These findings strongly indicate that Dub12 is an oncogene that, when

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constitutively expressed, can induce cytokine-independent growth in lymphocytes and may be implicated in leukemogenesis. It is likely that Dub2 controls cell growth by regulating the ubiquitin-dependent proteolysis or the ubiquitin-dependent state of a critical intracellular substrate. Functional similarity of the Dub11 and Dub12 would be expected. Thus, the biological role of Dub2 suggests similar important roles for the other Dub family members.

Screening for inhibitors of the DUB enzymes can also be easily accomplished using the known assays for activity. Such assays can be developed into high throughput screening efforts, testing, particularly, compounds known to affect protein turnover, or similar enzymatic sites. Small molecule antagonists of the enzymes, which will be membrane permeable, would be particularly desirable therapeutically.

In the MD embodiments of the present invention, mammalian, e.g., primate, and rodent, e.g., mouse, DNA sequences are provided encoding proteins which exhibit structural properties of ligands for proteins exhibiting a leucine-rich protein motif (LRR) that is important, e.g., in immune function. These proteins are designated herein human MD-1, human MD-2, and murine MD-2. The human MD-1 is a primate homolog of the previously described rodent MD-1, see, e.g., Miyake, et al. (1998) J. Immunol. 161:1348-1353, while human MD-2 and mouse MD-2 are newly discovered MD-1 homolog. For a general review of LRR proteins, see, e.g., Kobe and Deisenhofer (1994) Trends Biochem. Sci. 19:412. For the role of LRR in specific immune defenses, see, e.g., Jones, et al. (1994) Science 266:789; Dixon, et al. (1996) Cell 84:451; and Baker, et al. (1997) Science 276:726.

Similar sequences for proteins in other species should also be available. The descriptions below are directed, for exemplary purposes, to the primate, e.g., human, MD-1 and MD-2, and rodent, e.g., mouse, MD-2 natural alleles described, but are likewise applicable to allelic and/or polymorphic variants, e.g., from other individuals, as well as splicing variants, e.g., natural forms, and species variants.

The MD-1 or MD-2 proteins (naturally occurring or recombinant), fragments thereof, and antibodies thereto, along with compounds identified as having binding affinity to MD-1 or MD-2, should be useful in the treatment of conditions associated with abnormal physiology or development, such as, e.g., the recognition of specific pathogenic molecules and the activation of B cell physiology. As indicated above, MD-1 and MD-2 exhibit structural motifs characteristic of ligands for the RP105 or BAS-1 surface receptors. Thus, soluble forms, antibodies, or small molecule drugs which disrupt intercellular signaling mediated by these receptors, will find use in modulating cellular response. These responses will be important in normal or abnormal clinical situations.

The matching of the MD and RP105 may also be easily tested. Identification of the counter receptor for the MD-2 may include testing both the RP105 and BAS-1 genes, along with other screening methods, as described. The likely counter receptor structure for the MDs are RP105, BAS-1, and related genes. Associated proteins which bind to these, including the DUB proteins, may be identified using these techniques, among others.

Another aspect of the invention provides members of the cyclin proteins. The cyclins and their partner catalytic subunits, the cyclin-dependent kinases (Cdks), play key roles in the regulation of eukaryotic cell cycle events. See, e.g., Draetta (1994) Curr. Opin. Cell Biol. 6:842-846; Sherr (1994) Cell 79:551-555; and Ohtsubo, et al. (1995) Mol. Cell. Biol. 15:2612-2624. Cyclins were first identified in marine invertebrates on the basis of their dramatic cell cycle periodic expression during meiotic and mitotic divisions.

A large family of cyclins, designated cyclins A-H, bind and activate different Cdks which are serine/threonine kinases essential for cell cycle progression. The timing of the expression of the various cyclins is key in determining at which phase of the cell cycle (S, G₀, G₁, or G₂) their associated Cdk is active. D-type cyclins are synthesized early in G₁ and bind and activate CDK4 and CDK6. Cyclin E-Cdk2 and Cyclin A-Cdk2 complexes form later in G₁ as cells prepare to begin DNA synthesis. Cyclin

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B-cdc2 is active during G₂ and mitosis. See, e.g., Lees (1995) Curr. Opin. Cell Biol. 7:773-780.

Other Cyclin-Cdk complex associated proteins are critical for modulation of cyclin activity. Proteins that co-immunoprecipitated with cyclin E were visualized by SDS-PAGE. However, viability of the cyclin E "knockout" mouse, suggested the existence of redundancy. Moreover, work in other species also suggested that a homolog might exist in human.

Cdks can also exert control on cell division and proliferation by phosphorylating specific intracellular target proteins. This phosphorylation event can induce the cellular transition from the G₁ to the S phase of the cell cycle. See, e.g., Strahler, et al. (1992) Biochem. Biophys. Res. Comm. 185:197-203; Brattsand, et al. (1994) Eur. J. Biochem. 220:359-368; and Li, et al. (1996) Cell 85:319-329. Regulation of the cell cycle machinery is important in development and control of cellular proliferation. Misregulation may lead to proliferative disorders, e.g., neoplastic conditions and cancer. See, e.g., Sherr (1998) Science 274:1672-1677.

The novel cyclin gene, designated cyclin E2, exhibits about 49% structural identity to the known human cyclin E. See, e.g., Lew, et al. (1991) Cell 66:1197-1206; and NCBI Entrez accession number M74093. The new variant cyclin E2 sequences are provided in SEQ ID NO: 52 and SEQ ID NO: 53. Notable features on the E2 sequence include the cyclin box running from about residue 120-254; and a putative phosphorylation site at thr392. The phosphorylation site is trigger in cyclin E for ubiquitin dependent degradation. See Clurman, et al. (1996) Genes and Development 10:1979-1990. Particularly interesting segments include, e.g., from about 93-100; 98-106; 104-113; 107-121; 120-128; 124-134; 131-137; 172-177; 176-185; 189-193; 196-202; 200-210; 218-223; 228-232; 236-242; 240-245; and 248-252.

The structural homology of these genes to identified families suggests related function of these molecules. For example, PGT homologs should function in transport across cell membranes; TNF receptor family antagonists, or agonists, may act as a co-

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stimulatory molecule for regulation of T cell mediated cell activation, and may in fact, cause a shift of T helper cell types, e.g., between Th1 and Th2; chemokines have recognized functional properties; intracellular Dubs have been described and the role in oncogenesis established; membrane associated or soluble forms of signaling proteins such as the MDs are well known; and the role of cyclins in cell cycle regulation are recognized. Alternatively, the ligands or binding structures for the cell surface antigens may serve to regulate cell proliferation or development..

For the TNF ligand molecules, they typically modulate cell proliferation, viability, and differentiation. For example, TNF and FAS can kill cells expressing their respective receptors, including fibroblasts, liver cells, and lymphocytes. Some members of this class of ligands exhibit effects on cellular proliferation of cells expressing their respective receptors, e.g., B cells expressing CD40. These effects on proliferation may also effect subsequent differentiation steps, and may lead, directly or indirectly, to changes in cytokine expression profiles.

The members of the TNF ligand family also exhibit costimulation effects, which may also regulate cellular differentiation or apoptosis. Receptor expressing cells may be protected from activation induced cell death (AICD) or apoptosis. For example, CD40 ligand can have effects on T and B lymphocytes.

The embodiments characterized herein are mostly from human, but additional sequences for proteins in other mammalian species, e.g., primates and rodents, will also be available. See below. In particular, with the polypeptide sequences provided, reverse translation, e.g., using the genetic code, software is available, which will indicate what nucleic acid sequences could encode them. See, e.g., MacVector, Oxford Molecular Group Software. Thus, artificial genes, or redundant oligonucleotides may be selected to isolate natural variants or species counterparts.

II. Purified Protein

Primate, e.g., human, DC-PGT polypeptide sequence is shown in SEQ ID NO: 2; primate, e.g., human, HDTEA84 polypeptide sequence is shown in SEQ ID NO: 6; primate, e.g., human, HSLJD37R

polypeptide sequences are shown in SEQ ID NO: 8, 10, and 12; rodent, e.g., murine, RANKL polypeptide sequence is shown in SEQ ID NO: 17; primate forms of RANKL polypeptide sequence are shown in SEQ ID NO: 19, 21, and 23; primate, e.g., human, HCC5 chemokine polypeptide sequence is shown in SEQ ID NO: 25; primate, e.g., human, Dub11 polypeptide sequences are shown in SEQ ID NO: 32 and 34; primate, e.g., human, Dub12 polypeptide sequences are shown in SEQ ID NO: 36 and 38; primate, e.g., human, MD-1 polypeptide sequence is shown in SEQ ID NO: 42; primate, e.g., human, MD-2 polypeptide sequence is shown in SEQ ID NO: 44 and 46; rodent, e.g., mouse, MD-2 polypeptide sequences are shown in SEQ ID NO: 48 and 49; and primate, e.g., human, cyclin E2 is shown in SEQ ID NO: 54.

These amino acid sequences, provided amino to carboxy, are important in providing sequence information in the antigen allowing for distinguishing the protein from other proteins and exemplifying numerous variants. Moreover, the peptide sequences allow preparation of peptides to generate antibodies to recognize such segments, and nucleotide sequences allow preparation of oligonucleotide probes, both of which are strategies for detection or isolation, e.g., cloning, of genes or cDNAs encoding such sequences.

The purified protein, or proteins will typically comprise a plurality of distinct, e.g., nonoverlapping, segments of the specified length. Typically, the plurality will be at least two, more usually at least three, and preferably 5, 7, or even more. While the length minima are provided, longer lengths, of various sizes, may be appropriate, e.g., one of length 7, and two of length 12. Such peptides are useful for generating antibodies by standard methods, as described herein. Synthetic peptides or purified protein can be presented to an immune system to generate a specific binding composition, e.g., monoclonal or polyclonal antibodies. See, e.g., Coligan (1991) Current Protocols in Immunology Wiley/Greene; and Harlow and Lane (Current ed.) Antibodies: A Laboratory Manual Cold Spring Harbor Press.

For example, the specific binding composition could be used for screening of an expression library made from a cell line which

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expresses a clone encoding, e.g., a prostaglandin transporter. The screening can be standard staining of surface expressed protein, or by panning. Screening of intracellular expression can also be performed by various staining or immunofluorescence procedures. The binding compositions could be used to affinity purify or sort out cells expressing the protein. The binding compositions may also be useful in determining qualitative and quantitative expression levels of the proteins in various biological samples, including, e.g., cell types or tissues.

As used herein, the term, e.g., "human DC-PGT", shall encompass, when used in a protein context, a protein having amino acid sequence shown in SEQ ID NO: 2. Significant polypeptide fragments of such a protein should preserve some of the properties, biological or physical, of the full length protein. Other essentially identical or equivalent proteins may be found in other primates or related species. In addition, binding components, e.g., antibodies, typically bind to, e.g., a DC-PGT, with high affinity, e.g., at least about 100 nM, usually better than about 30 nM, preferably better than about 10 nM, and more preferably at better than about 3 nM. Homologous proteins would be found in mammalian species other than human, e.g., primates or rodents. Non-mammalian species should also possess structurally or functionally related genes and proteins, e.g., birds or amphibians. Similar meanings apply in reference to HDTEA84, HSLJD37R, RANKL, HCC5, Dub11, Dub12, MD-1, MD-2, and cyclin E2.

The term polypeptide, as used herein, includes a significant fragment or segment, and encompasses a stretch of amino acid residues of at least about 8 amino acids, generally at least 10 amino acids, more generally at least 12 amino acids, often at least 14 amino acids, more often at least 16 amino acids, typically at least 18 amino acids, more typically at least 20 amino acids, usually at least 22 amino acids, more usually at least 24 amino acids, preferably at least 26 amino acids, more preferably at least 28 amino acids, and, in particularly preferred embodiments, at least about 30 or more amino acids. The segments may have lengths of at least 37, 45, 53, 61, 70, 80, 90, etc., and often will encompass a plurality of such matching sequences. The

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specific ends of such a segment will be at any combinations within the protein. In certain embodiments, there will be a plurality of distinct, e.g., nonoverlapping, segments of the specified length. Typically, the plurality will be at least two, more usually at
5 least three, and preferably 5, 7, or even more. While the length minima are provided, longer lengths, of various sizes, may be appropriate, e.g., one of length 7, and two of length 12.

The term "binding composition" refers to molecules that bind with specificity to the respective protein or polypeptide, e.g.,
10 DC-PGT, e.g., in a cell adhesion pairing type fashion, or an antibody-antigen interaction. Other compounds include, e.g., proteins, which specifically associate with DC-PGT, including in a natural physiologically relevant protein-protein interaction, either covalent or non-covalent. The molecule may be a polymer,
15 or chemical reagent. A functional analog may be an antigen with structural modifications, or it may be a molecule which has a molecular shape which interacts with the appropriate binding determinants. The compounds may serve as agonists or antagonists of the binding interaction, see, e.g., Goodman, et al. (eds. 1990)
20 Goodman & Gilman's: The Pharmacological Bases of Therapeutics (8th ed.) Pergamon Press.

Substantially pure, in the polypeptide context, typically means that the protein is free from other contaminating proteins, nucleic acids, and other biologicals derived from the original
25 source organism or cell. Purity may be assayed by standard methods, and will ordinarily be at least about 40% pure, more ordinarily at least about 50% pure, generally at least about 60% pure, more generally at least about 70% pure, often at least about 75% pure, more often at least about 80% pure, typically at least
30 about 85% pure, more typically at least about 90% pure, preferably at least about 95% pure, more preferably at least about 98% pure, and in most preferred embodiments, at least 99% pure. The analysis may be weight or molar percentages, evaluated, e.g., by gel staining, spectrophotometry, or terminus labeling. Carriers
35 or excipients will often be subsequently added.

Solubility of a polypeptide or fragment depends upon the environment and the polypeptide. Many parameters affect

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polypeptide solubility, including temperature, electrolyte environment, size and molecular characteristics of the polypeptide, and nature of the solvent. Typically, the temperature at which the polypeptide is used ranges from about 4°
5 C to about 65° C. Usually the temperature at use is greater than about 18° C. For diagnostic purposes, the temperature will usually be about room temperature or warmer, but less than the denaturation temperature of components in the assay. For
10 therapeutic purposes, the temperature will usually be body temperature, typically about 37° C for humans and mice, though under certain situations the temperature may be raised or lowered in situ or in vitro.

The size and structure of the polypeptide should generally be in a substantially stable state, and usually not in a denatured
15 state. The polypeptide may be associated with other polypeptides in a quaternary structure, e.g., to confer solubility, or associated with lipids or detergents in a manner which approximates natural lipid bilayer interactions.

The solvent and electrolytes will usually be a biologically
20 compatible buffer, of a type used for preservation of biological activities, and will usually approximate a physiological aqueous solvent. Usually the solvent will have a neutral pH, typically between about 5 and 10, and preferably about 7.5. On some occasions, one or more detergents will be added, typically a mild
25 non-denaturing one, e.g., CHS (cholesteryl hemisuccinate) or CHAPS (3-[3-cholamidopropyl]dimethylammonio]-1-propane sulfonate), or a low enough concentration as to avoid significant disruption of structural or physiological properties of the protein.

Solubility is reflected by sedimentation measured in Svedberg
30 units, which are a measure of the sedimentation velocity of a molecule under particular conditions. The determination of the sedimentation velocity was classically performed in an analytical ultracentrifuge, but is typically now performed in a standard ultracentrifuge. See, Freifelder (1982) Physical Biochemistry (2d
35 ed.), W.H. Freeman; and Cantor and Schimmel (1980) Biophysical Chemistry, parts 1-3, W.H. Freeman & Co., San Francisco; each of which is hereby incorporated herein by reference. As a crude

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determination, a sample containing a putatively soluble polypeptide is spun in a standard full sized ultracentrifuge at about 50K rpm for about 10 minutes, and soluble molecules will remain in the supernatant. A soluble particle or polypeptide will typically be less than about 30S, more typically less than about 15S, usually less than about 10S, more usually less than about 6S, and, in particular embodiments, preferably less than about 4S, and more preferably less than about 3S.

The human complimentary DNA and deduced amino acid sequence provided here for DC-PGT contains sequences corresponding to twelve putative transmembrane (TM) segments, based upon a hydropathicity and structural analysis of DC-PGT. A TopPredII (Claros and von Heijne (1994) Comp. Applic. Biosci. 10:685-686) profile of the DC-PGT sequence showing peaks that reach beyond 'putative' or 'certain' baselines. The 12 transmembrane segments correspond to hydrophobic stretches which run approximately from amino acids 47-68 (TM1); 88-107 (TM2); 117-136 (TM3); 188-208 (TM4); 225-244 (TM5); 279-294 (TM6) 367-386 (TM7); 412-431 (TM8); 450-474 (TM9); 561-578 (TM10); 597-616 (TM11); and 651-675 (TM12). Charged amino residues located within the transmembrane domains are: glutamine at amino residues 59, 62, 196, 207, 380, 469, 602, 655, and 675; glutamic acid at residue 95; and arginine at residues 607 and 674. Extracellular loops correspond approximately to amino acid residues 69-87, 137-187, 295-366, 432-449, 579-596, and 617-650. Putative N-glycosylation sites in the exposed, extracellular face of the molecule are located in the second and fifth extracellular loops at Asn-X-Ser/Thr motifs (e.g., 146-148; 176-178; and 538-540). Intracellular portions correspond approximately to amino acid residues 1-46, 108-116, 209-224, 295-366, 432-449, 579-596, and 676-709. These boundaries will often be the boundaries of segments of interest, which be include multiple described segments.

Transporters of this family are typically 12 transmembrane proteins of approximately 650 amino acids in length and include the organic anion transporters in man and rat, prostaglandin transporters of man (Lu, et al. (1996) J. Clin. Invest. 98:1142-1149) and rat; brain digoxin transporters and Matrin F/G of rat

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(Kanai, et. al. (1995) Science 268:866-869). Characteristic of this family of organic anion transporter proteins is a cysteine rich region located in one of the extracellular loops, which resembles a zinc finger motif. The DC-PGT cysteine rich region is located in extracellular loop 5 with cysteines approximately at positions 489, 493, 495, 504, 516, 520, 539, 541, 554, and 557.

Other particularly interesting segments of the TNF receptors, Dubs, MDs, and cyclin E are pointed out. These may also be segments of comparison with other proteins or genes.

III. Physical Variants

This invention also encompasses proteins or peptides having substantial amino acid sequence homology with the amino acid sequences of the described proteins. The variants include species and polymorphic variants, e.g., naturally occurring forms.

Amino acid sequence homology, or sequence identity, is determined by optimizing residue matches, if necessary, by introducing gaps as required. See also Needleham, et al. (1970) J. Mol. Biol. 48:443-453; Sankoff, et al. (1983) Chapter One in Time Warps, String Edits, and Macromolecules: The Theory and Practice of Sequence Comparison, Addison-Wesley, Reading, MA; and software packages from IntelliGenetics, Mountain View, CA; and the University of Wisconsin Genetics Computer Group, Madison, WI. Sequence identity changes when considering conservative substitutions as matches. Conservative substitutions typically include substitutions within the following groups: glycine, alanine; valine, isoleucine, leucine; aspartic acid, glutamic acid; asparagine, glutamine; serine, threonine; lysine, arginine; and phenylalanine, tyrosine. Homologous amino acid sequences are typically intended to include natural polymorphic or allelic and interspecies variations in each respective protein sequence. Typical homologous proteins or peptides will have from 25-100% identity (if gaps can be introduced), to 50-100% identity (if conservative substitutions are included) with the amino acid sequence of the HDTEA84. Identity measures will be at least about 35%, generally at least about 40%, often at least about 50%, typically at least about 60%, usually at least about 70%.

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preferably at least about 80%, and more preferably at least about 90%.

For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When
5 using a sequence comparison algorithm, test and reference sequences are input into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. The sequence comparison algorithm then calculates the percent sequence identity for the test sequence(s)
10 relative to the reference sequence, based on the designated program parameters.

Optical alignment of sequences for comparison can be conducted, e.g., by the local homology algorithm of Smith and Waterman (1981) Adv. Appl. Math. 2:482, by the homology alignment
15 algorithm of Needleman and Wunsch (1970) J. Mol. Biol. 48:443, by the search for similarity method of Pearson and Lipman (1988) Proc. Nat'l Acad. Sci. USA 85:2444, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics
20 Computer Group, 575 Science Dr., Madison, WI), or by visual inspection (see generally Ausubel et al., supra).

One example of a useful algorithm is PILEUP. PILEUP creates a multiple sequence alignment from a group of related sequences using progressive, pairwise alignments to show relationship and
25 percent sequence identity. It also plots a tree or dendrogram showing the clustering relationships used to create the alignment. PILEUP uses a simplification of the progressive alignment method of Feng and Doolittle (1987) J. Mol. Evol. 35:351-360. The method used is similar to the method described by Higgins and Sharp
30 (1989) CABIOS 5:151-153. The program can align up to 300 sequences, each of a maximum length of 5,000 nucleotides or amino acids. The multiple alignment procedure begins with the pairwise alignment of the two most similar sequences, producing a cluster of two aligned sequences. This cluster is then aligned to the
35 next most related sequence or cluster of aligned sequences. Two clusters of sequences are aligned by a simple extension of the pairwise alignment of two individual sequences. The final

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alignment is achieved by a series of progressive, pairwise alignments. The program is run by designating specific sequences and their amino acid or nucleotide coordinates for regions of sequence comparison and by designating the program parameters.

- 5 For example, a reference sequence can be compared to other test sequences to determine the percent sequence identity relationship using the following parameters: default gap weight (3.00), default gap length weight (0.10), and weighted end gaps.

Another example of algorithm that is suitable for determining
10 percent sequence identity and sequence similarity is the BLAST algorithm, which is described Altschul, et al. (1990) J. Mol. Biol. 215:403-410. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (<http://www.ncbi.nlm.nih.gov/>). This algorithm involves
15 first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score
20 threshold (Altschul, et al., supra). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are then extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Extension of the word hits in
25 each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The
30 BLAST program uses as defaults a wordlength (W) of 11, the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) Proc. Nat'l Acad. Sci. USA 89:10915) alignments (B) of 50, expectation (E) of 10, M=5, N=4, and a comparison of both strands.

- 35 In addition to calculating percent sequence identity, the BLAST algorithm also performs a statistical analysis of the similarity between two sequences (see, e.g., Karlin and Altschul

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(1993) Proc. Nat'l Acad. Sci. USA 90:5873-5787). One measure of similarity provided by the BLAST algorithm is the smallest sum probability ($P(N)$), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is less than about 0.1, more preferably less than about 0.01, and most preferably less than about 0.001.

A further indication that two nucleic acid sequences of polypeptides are substantially identical is that the polypeptide encoded by the first nucleic acid is immunologically cross reactive with the polypeptide encoded by the second nucleic acid, as described below. Thus, a polypeptide is typically substantially identical to a second polypeptide, for example, where the two peptides differ only by conservative substitutions. Another indication that two nucleic acid sequences are substantially identical is that the two molecules hybridize to each other under stringent conditions, as described below.

The isolated DC-PGT, HDTEA84, HSLJD37R, RANKL, HCC5, Dub, MD-1, MD-2, or cyclin E2 DNAs can be readily modified by nucleotide substitutions, nucleotide deletions, nucleotide insertions, and inversions of nucleotide stretches. These modifications result in novel DNA sequences which encode these antigens, their derivatives, or proteins having similar physiological, immunogenic, antigenic, or other functional activity. These modified sequences can be used to produce mutant antigens or to enhance expression. Enhanced expression may involve gene amplification, increased transcription, increased translation, and other mechanisms. For example, "Mutant HDTEA84" encompasses a polypeptide otherwise falling within the sequence identity definition of the HDTEA84 as set forth above, but having an amino acid sequence which differs from that of HDTEA84 as normally found in nature, whether by way of deletion, substitution, or insertion. This generally includes proteins having significant identity with a protein having sequence of SEQ ID NO: 6, and as sharing various biological activities, e.g., antigenic or immunogenic, with those

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sequences, and in preferred embodiments contain most of the full length disclosed sequences. Full length sequences will typically be preferred, though truncated versions, e.g., soluble constructs and intact domains, will also be useful, likewise, genes or
5 proteins found from natural sources are typically most desired. Similar concepts apply to different HDTEA84 proteins, particularly those found in various warm blooded animals, e.g., mammals and birds, or fish. These descriptions are generally meant to encompass all HDTEA84 proteins, not limited to the particular
10 human embodiment specifically discussed. Similar concepts apply to the other polypeptides provided.

DC-PGT, HDTEA84, HSLJD37R, RANKL, HCC5, Dub, MD-1, MD-2, or cyclin E2 mutagenesis can also be conducted by making amino acid insertions or deletions. Although site specific mutation sites
15 are predetermined, mutants need not be site specific. Protein mutagenesis can be conducted by making amino acid insertions or deletions, or combinations may be generated to arrive at a final construct. Insertions include amino- or carboxy- terminal fusions. Random mutagenesis can be conducted at a target codon
20 and the expressed mutants can then be screened for the desired activity. Methods for making substitution mutations at predetermined sites in DNA having a known sequence are well known in the art, e.g., by M13 primer mutagenesis or polymerase chain reaction (PCR) techniques. See, e.g., Sambrook, et al. (1989);
25 Ausubel, et al. (1987 and Supplements); and Kunkel, et al. (1987) Methods in Enzymol. 154:367-382.

The mutations in the DNA normally should not place coding sequences out of reading frames and preferably will not create complementary regions that could hybridize to produce secondary
30 mRNA structure such as loops or hairpins.

The present invention also provides recombinant proteins, e.g., heterologous fusion proteins using segments from these proteins. A heterologous fusion protein is a fusion of proteins or segments which are naturally not normally fused in the same
35 manner. Thus, the fusion product of an immunoglobulin with a polypeptide is a continuous protein molecule having sequences fused in a typical peptide linkage, typically made as a single

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translation product and exhibiting properties derived from each source peptide. A similar concept applies to heterologous nucleic acid sequences.

5 The present invention also provides recombinant proteins, e.g., heterologous fusion proteins using segments from these proteins. A heterologous fusion protein is a fusion of proteins or segments which are naturally not normally fused in the same manner. A similar concept applies to heterologous nucleic acid sequences. Fusion proteins will be useful as sources for
10 cleaving, separating, and purifying portions thereof.

In addition, new constructs may be made from combining similar functional domains from other proteins. For example, target-binding or other segments may be "swapped" between different new fusion polypeptides or fragments. See, e.g.,
15 Cunningham, et al. (1989) Science 243:1330-1336; and O'Dowd, et al. (1988) J. Biol. Chem. 263:15985-15992.

The phosphoramidite method described by Beaucage and Carruthers (1981) Tetra. Letts. 22:1859-1862, will produce suitable synthetic DNA fragments. A double stranded fragment will
20 often be obtained either by synthesizing the complementary strand and annealing the strand together under appropriate conditions or by adding the complementary strand using DNA polymerase with an appropriate primer sequence, e.g., PCR techniques.

25 IV. Functional Variants

The blocking of physiological response with, e.g., HDTEA84, HSLJD37R, RANKL, HCC5 chemokine, MD-1, or MD-2, may result from the inhibition of binding of the respective ligand to signaling form of receptor or binding counterstructure, e.g., through
30 competitive inhibition. In others, binding affinity to substrate may be modifiable or competed with, e.g., DC-PGT, Dubs, or cyclin E2. Thus, in vitro assays of the present invention will often use isolated protein, soluble fragments comprising ligand or substrate binding segments of these proteins, or forms attached to solid
35 phase substrates. These assays will also allow for the diagnostic determination of the effects of either binding segment mutations

and modifications, or antigen mutations and modifications, e.g., HDTEA84, HSLJD37R, RANKL, MD-1, or MD-2 analogs.

This invention also contemplates the use of competitive drug screening assays, e.g., where neutralizing antibodies to antigen or binding fragments compete with a test compound for binding to the protein, e.g., of natural protein sequence. This is applicable to substrate binding, e.g., competitive inhibitors, and in receptor interaction, where the protein has a binding counterstructure.

"Derivatives" of , e.g., receptor, antigens include amino acid sequence mutants from naturally occurring forms, glycosylation variants, and covalent or aggregate conjugates with other chemical moieties. Covalent derivatives can be prepared by linkage of functionalities to groups which are found in receptor amino acid side chains or at the N- or C- termini, e.g., by standard means. See, e.g., Lundblad and Noyes (1988) Chemical Reagents for Protein Modification, vols. 1-2, CRC Press, Inc., Boca Raton, FL; Hugli (ed. 1989) Techniques in Protein Chemistry, Academic Press, San Diego, CA; and Wong (1991) Chemistry of Protein Conjugation and Cross Linking, CRC Press, Boca Raton, FL.

In particular, glycosylation alterations are included, e.g., made by modifying the glycosylation patterns of a polypeptide during its synthesis and processing, or in further processing steps. See, e.g., Elbein (1987) Ann. Rev. Biochem. 56:497-534.

Also embraced are versions of the peptides with the same primary amino acid sequence which have other minor modifications, including phosphorylated amino acid residues, e.g., phosphotyrosine, phosphoserine, or phosphothreonine.

Fusion polypeptides between these proteins and other homologous or heterologous proteins are also provided. Many cytokine receptors or other surface proteins are multimeric, e.g., homodimeric entities, and a repeat construct may have various advantages, including lessened susceptibility to proteolytic cleavage. Typical examples are fusions of a reporter polypeptide, e.g., luciferase, with a segment or domain of a protein, e.g., a receptor-binding segment, so that the presence or location of the fused ligand may be easily determined. See, e.g., Dull, et al.,

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U.S. Patent No. 4,859,609. Other gene fusion partners include bacterial β -galactosidase, trpE, Protein A, β -lactamase, alpha amylase, alcohol dehydrogenase, yeast alpha mating factor, and detection or purification tags such as a FLAG sequence of His6
5 sequence. See, e.g., Godowski, et al. (1988) Science 241:812-816. Of particular interest are fusion constructs of receptor with a membrane attachment domain.

Fusion peptides will typically be made by either recombinant nucleic acid methods or by synthetic polypeptide methods.

10 Techniques for nucleic acid manipulation and expression are described generally, e.g., in Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual (2d ed.), vols. 1-3, Cold Spring Harbor Laboratory; and Ausubel, et al. (eds. 1993) Current Protocols in Molecular Biology, Greene and Wiley, NY. Techniques
15 for synthesis of polypeptides are described, e.g., in Merrifield (1963) J. Amer. Chem. Soc. 85:2149-2156; Merrifield (1986) Science 232: 341-347; Atherton, et al. (1989) Solid Phase Peptide Synthesis: A Practical Approach, IRL Press, Oxford; and Grant (1992) Synthetic Peptides: A User's Guide, W.H. Freeman, NY.

20 This invention also contemplates the use of derivatives of the proteins other than variations in amino acid sequence or glycosylation. Such derivatives may involve covalent or aggregative association with chemical moieties. Covalent or aggregative derivatives will be useful as immunogens, as reagents
25 in immunoassays, or in purification methods such as for affinity purification of binding partners, e.g., other antigens. The desired proteins can be immobilized by covalent bonding to a solid support such as cyanogen bromide-activated SEPHAROSE, by methods which are well known in the art, or adsorbed onto polyolefin
30 surfaces, with or without glutaraldehyde cross-linking, for use in the assay or purification of antibodies or an alternative binding composition. The protein can also be labeled with a detectable group, e.g., for use in diagnostic assays. Purification may be effected by an immobilized antibody or complementary binding
35 partner. Conversely, immunoabsorption or immunodepletion techniques may be developed.

A solubilized protein or fragment of this invention can be used as an immunogen for the production of antisera or antibodies specific for binding to the antigen or fragments thereof. Purified antigen can be used to screen monoclonal antibodies or antigen-binding fragments, encompassing antigen binding fragments of natural antibodies, e.g., Fab, Fab', F(ab)₂, etc. Purified protein can also be used as a reagent to detect antibodies generated in response to the presence of elevated levels of the antigen or cell fragments containing the antigen, both of which may be diagnostic of an abnormal or specific physiological or disease condition. This invention contemplates antibodies raised against amino acid sequences encoded by nucleotide sequences described, or fragments of proteins containing it. In particular, this invention contemplates antibodies having binding affinity to or being raised against specific fragments, e.g., which are predicted to lie outside of the lipid bilayer, both extracellular or intracellular.

The present invention contemplates the isolation of additional closely related species variants. Southern and Northern blot analysis should establish that similar genetic entities exist in other mammals. It is likely that these proteins are widespread in species variants, e.g., rodents, lagomorphs, carnivores, artiodactyla, perissodactyla, and primates.

The invention also provides means to isolate a group of related antigens displaying both distinctness and similarities in structure, expression, and function. Elucidation of many of the physiological effects of the molecules will be greatly accelerated by the isolation and characterization of additional distinct species variants of them. In particular, the present invention provides useful probes for identifying additional homologous genetic entities in different species.

The isolated genes will allow transformation of cells lacking expression of a corresponding protein, e.g., either species types or cells which lack corresponding antigens and exhibit negative background activity. This should allow analysis of the function of genes in comparison to untransformed control cells.

Dissection of critical structural elements which effect the various activation or differentiation functions mediated through these antigens is possible using standard techniques of modern molecular biology, particularly in comparing members of the related class. See, e.g., the homolog-scanning mutagenesis technique described in Cunningham, et al. (1989) Science 243:1339-1336; and approaches used in O'Dowd, et al. (1988) J. Biol. Chem. 263:15985-15992; and Lechleiter, et al. (1990) EMBO J. 9:4381-4390.

The invention also provides, in the context of the DC-PGT, means to isolate a group of related organic anion transporters, e.g., other vertebrate prostaglandin transporters, displaying both distinctness and similarities in structure, expression, and function. Elucidation of many of the physiological effects of the antigens will be greatly accelerated by the isolation and characterization of distinct species variants. In particular, the present invention provides useful probes for identifying additional homologous genetic entities in different species. The results described above indicate that sufficiently homologous genes exist in other species that cross-species hybridization is likely to allow successful cloning.

The isolated genes will allow transformation of cells lacking expression of a described gene, e.g., prostaglandin transporter. Various species types or cells which lack corresponding proteins can be isolated, and should exhibit negative background activity. Expression of transformed genes will allow isolation of antigenically pure cell lines, with defined or single specie variants. This approach will allow for more sensitive detection and discrimination of the physiological effects of the gene, e.g., prostaglandin transporters. Subcellular fragments, e.g., cytoplasts or membrane fragments, can be isolated and used.

The DC-PGT genes may also be useful to increase the rate of transport of desired prostaglandins into transformed cells. Thus, the transporter may be transformed into cells for targeting of incorporation of desired substrates or analogs. For instance, it may be useful to incorporate specific modified prostaglandins into those cells, which may become more susceptible to other

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treatments, or directly affected. Thus, specific dendritic cell subsets may be transformed to become more sensitive to prostaglandins or specific substrates. Conversely, such cells may be useful screening targets to identify entities which can block transport, thereby preventing uptake of substrate.

Structural studies of the transporter will lead to design of new variants, particularly analogs exhibiting modified binding affinity, or perhaps, altered rate of transporter activity. This can be combined with previously described screening methods to isolate variants exhibiting desired spectra of activities. Alternatively, many different prostaglandins and analogs thereof may be screened for either transporter binding affinity or transporter transfer. The transporter may require a direct energy source, e.g., ATP or other nucleotide triphosphate, or may depend upon an ion gradient, as described above.

In the context of the Dubs and cyclin E2, intracellular functions would probably involve segments of the antigen which are normally accessible to the cytosol, as would segments of the receptors. However, protein internalization may occur under certain circumstances, and interaction between intracellular components and "extracellular" components may occur. The specific segments of interaction of protein with other intracellular components may be identified by mutagenesis or direct biochemical means, e.g., cross-linking or affinity methods.

Structural analysis by crystallographic or other physical methods will also be applicable. Further investigation of the mechanism of signal transduction will include study of associated components which may be isolatable by affinity methods or by genetic means, e.g., complementation analysis of mutants.

Further study of the expression and control of the proteins will be pursued. The controlling elements associated with the antigens should exhibit differential physiological, developmental, tissue specific, or other expression patterns. Upstream or downstream genetic regions, e.g., control elements, are of interest. In particular, physiological or developmental variants, e.g., multiple alternatively processed forms of the antigen might be found. Thus, differential splicing of message may lead to an

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assortment of membrane bound forms, soluble forms, and modified versions of antigen.

Structural studies of the antigens will lead to design of new antigens, particularly analogs exhibiting agonist or antagonist properties on the molecule. This can be combined with previously described screening methods to isolate antigens exhibiting desired spectra of activities.

V. Antibodies

Antibodies can be raised to the various described polypeptides, including species, polymorphic, or allelic variants, and fragments thereof, both in their naturally occurring forms and in their recombinant forms. Additionally, antibodies can be raised to the proteins in either their active forms or in their inactive forms, including native or denatured versions. Anti-idiotypic antibodies are also contemplated.

Antibodies, including binding fragments and single chain versions, against predetermined fragments of the antigens can be raised by immunization of animals with conjugates of the fragments with immunogenic proteins. Monoclonal antibodies are prepared from cells secreting the desired antibody. These antibodies can be screened for binding to normal or defective polypeptide, or screened for agonistic or antagonistic activity. Antibodies may be agonistic or antagonistic, e.g., by sterically blocking partner or substrate binding. These monoclonal antibodies will usually bind with at least a K_D of about 1 mM, more usually at least about 300 μ M, typically at least about 100 μ M, more typically at least about 30 μ M, preferably at least about 10 μ M, and more preferably at least about 3 μ M or better. More preferred embodiments may have even higher affinities, e.g., at least 300 nM, 30 nM, 3 nM, or perhaps even picomolar affinity.

The term "binding composition" refers to molecules that bind with affinity and selectivity to, e.g., the DC-PGT, e.g., in an antibody-antigen interaction. However, other compounds, e.g., accessory proteins, may also specifically and/or selectively associate with the antigen to the exclusion of other molecules. Typically, the association will be in a natural physiologically

relevant protein-protein interaction, either covalent or non-covalent, and may include members of a multiprotein complex, including carrier compounds or dimerization partners. The molecule may be a polymer, or chemical reagent. No implication as to whether an antigen is necessarily a convex shaped molecule, e.g., the ligand or the receptor of a ligand-receptor interaction, is necessarily represented, other than whether the interaction exhibits similar specificity, e.g., specific or selective affinity. A functional analog may be a polypeptide with structural modifications, e.g., a mutein, or may be a wholly unrelated molecule, e.g., which has a molecular shape which interacts with the appropriate ligand binding determinants. The ligands may serve as agonists or antagonists of the receptor, see, e.g., Goodman, et al. Goodman & Gilman's: The Pharmacological Bases of Therapeutics (current edition) Pergamon Press, Tarrytown, N.Y.

The term "binding agent:antigen complex", as used herein, refers to a complex of a binding agent and antigen, e.g., a DC-PGT protein, that is formed by specific binding of the binding agent to antigen. Specific or selective binding of the binding agent means that the binding agent has a specific binding site, e.g., antigen binding site, that recognizes a site on the antigen. For example, antibodies raised to a DC-PGT protein and recognizing an epitope on the protein are capable of forming a binding agent:DC-PGT protein complex by specific selective binding. Typically, the formation of a binding agent:DC-PGT protein complex allows the qualitative or quantitative measurement of DC-PGT protein in a mixture of other proteins and biologics. The term "antibody:DC-PGT protein complex" refers to an embodiment in which the binding agent, e.g., is the antigen binding portion from an antibody. The antibody may be monoclonal, polyclonal, or a binding fragment of an antibody, e.g., an Fab or F(ab)2 fragment. The antibody will preferably be a polyclonal antibody for cross-reactivity testing purposes.

The phrase "specifically binds to an antibody" or "specifically immunoreactive with", when referring to a protein or peptide, refers to a binding reaction which is determinative of

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the presence of the protein in the presence of a heterogeneous population of other proteins and other biological components. Thus, under designated immunoassay conditions, the specified antibodies bind to a particular protein and do not significantly
5 bind other proteins present in the sample. Specific binding to an antibody under such conditions may require an antibody that is selected for its specificity or selectivity for a particular protein. Often, the serum can be immunoselected or immunodepleted, to minimize crossreactivity with a specific target
10 protein.

A DC-PGT polypeptide that specifically binds to, or that is specifically immunoreactive with, an antibody, e.g., such as a polyclonal antibody, generated against a defined immunogen, e.g., such as an immunogen consisting of an amino acid sequence of SEQ
15 ID NO: 2, or fragments thereof, or a polypeptide generated from the nucleic acid of SEQ ID NO: 1 is typically determined in an immunoassay. Included within the metes and bounds of the present invention are those nucleic acid sequences described herein, including functional variants, that encode polypeptides that
20 selectively bind to polyclonal antibodies generated against the prototypical DC-PGT polypeptide as structurally and functionally defined herein. The immunoassay typically uses a polyclonal antiserum which was raised, e.g., to a protein of SEQ ID NO: 2. This antiserum is selected to have low crossreactivity against
25 appropriate other PGT family members, preferably from the same species, and any such crossreactivity is removed by immunoabsorption prior to use in the immunoassay. Appropriate selective serum preparations can be isolated, and characterized.

The purified protein or defined peptides are useful for
30 generating antibodies by standard methods, as described above. Synthetic peptides or purified protein can be presented to an immune system to generate monoclonal or polyclonal antibodies. See, e.g., Coligan (1991) Current Protocols in Immunology Wiley/Greene; and Harlow and Lane (1989) Antibodies: A Laboratory
35 Manual, Cold Spring Harbor Press. Alternatively, the HDTEA84 can be used as a specific binding reagent, and advantage can be taken

of its specificity of binding, much like an antibody would be used.

For example, the specific binding composition could be used for screening of an expression library made from a cell line which expresses an HDTEA84, HSLJD37R, or RANKL. The screening can be standard staining of surface expressed antigen constructs, or by panning. Screening of intracellular expression can also be performed by various staining or immunofluorescence procedures. The binding compositions could be used to affinity purify or sort out cells expressing the protein.

In order to produce antisera for use in an immunoassay, the protein, e.g., of SEQ ID NO: 2, is isolated as described herein. For example, recombinant protein may be produced in a mammalian cell line. An appropriate host, e.g., an inbred strain of mice such as Balb/c, is immunized with the protein of SEQ ID NO: 2 using a standard adjuvant, such as Freund's adjuvant, and a standard mouse immunization protocol (see Harlow and Lane). Alternatively, a substantially full length synthetic peptide derived from the sequences disclosed herein can be used as an immunogen. Polyclonal sera are collected and titered against the immunogen protein in an immunoassay, e.g., a solid phase immunoassay with the immunogen immobilized on a solid support. Polyclonal antisera with a titer of 10^4 or greater are selected and tested for their cross reactivity against other PGT family members, e.g., human or rat PGT, using a competitive binding immunoassay such as the one described in Harlow and Lane, supra, at pages 570-573. Preferably at least two PGT family members are used in this determination in conjunction with the target. These PGT family members can be produced as recombinant proteins and isolated using standard molecular biology and protein chemistry techniques as described herein. Thus, antibody preparations can be identified or produced having desired selectivity or specificity for subsets of PGT family members.

Immunoassays in the competitive binding format can be used for the crossreactivity determinations. For example, the protein of SEQ ID NO: 2 can be immobilized to a solid support. Proteins added to the assay compete with the binding of the antisera to the

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immobilized antigen. The ability of the above proteins to compete with the binding of the antisera to the immobilized protein is compared to the protein of SEQ ID NO: 2. The percent crossreactivity for the above proteins is calculated, using
5 standard calculations. Those antisera with less than 10% crossreactivity with each of the proteins listed above are selected and pooled. The cross-reacting antibodies are then removed from the pooled antisera by immunoabsorption or immunodepletion with the above-listed proteins.

10 The immunoabsorbed and pooled antisera are then used in a competitive binding immunoassay as described above to compare a second protein to the immunogen protein. In order to make this comparison, the two proteins are each assayed at a wide range of concentrations and the amount of each protein required to inhibit
15 50% of the binding of the antisera to the immobilized protein is determined. If the amount of the second protein required is less than twice the amount of the protein of, e.g., SEQ ID NO: 2 that is required, then the second protein is said to specifically bind to an antibody generated to the immunogen.

20 The antibodies of this invention can also be useful in diagnostic applications. As capture or non-neutralizing antibodies, they can be screened for ability to bind to the antigens without inhibiting binding by a partner. As neutralizing antibodies, they can be useful in competitive binding assays.

25 They will also be useful in detecting or quantifying a described protein or its binding partners. See, e.g., Chan (ed. 1987) Immunology: A Practical Guide, Academic Press, Orlando, FL; Price and Newman (eds. 1991) Principles and Practice of Immunoassay, Stockton Press, N.Y.; and Ngo (ed. 1988) Nonisotopic Immunoassay,
30 Plenum Press, N.Y. Cross absorptions or depletions and other tests will identify antibodies which exhibit various spectra of specificities, e.g., unique or shared species specificities.

Further, the antibodies, including antigen binding fragments, of this invention can be potent antagonists that bind to the
35 antigen and inhibit functional binding or inhibit the ability of a binding partner to elicit a biological response. They also can be useful as non-neutralizing antibodies and can be coupled to toxins

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or radionuclides so that when the antibody binds to antigen, a cell expressing it, e.g., on its surface, is killed. Further, these antibodies can be conjugated to drugs or other therapeutic agents, either directly or indirectly by means of a linker, and may effect drug targeting. They may be labeled for histology evaluation.

Antigen fragments may be joined to other materials, particularly polypeptides, as fused or covalently joined polypeptides to be used as immunogens. An antigen and its fragments may be fused or covalently linked to a variety of immunogens, such as keyhole limpet hemocyanin, bovine serum albumin, tetanus toxoid, etc. See Microbiology, Hoeber Medical Division, Harper and Row, 1969; Landsteiner (1962) Specificity of Serological Reactions, Dover Publications, New York; Williams, et al. (1967) Methods in Immunology and Immunochemistry, vol. 1, Academic Press, New York; and Harlow and Lane (1988) Antibodies: A Laboratory Manual, CSH Press, NY, for descriptions of methods of preparing polyclonal antisera.

In some instances, it is desirable to prepare monoclonal antibodies from various mammalian hosts, such as mice, rodents, primates, humans, etc. Description of techniques for preparing such monoclonal antibodies may be found in, e.g., Stites, et al. (eds.) Basic and Clinical Immunology (4th ed.), Lange Medical Publications, Los Altos, CA, and references cited therein; Harlow and Lane (1988) Antibodies: A Laboratory Manual, CSH Press; Goding (1986) Monoclonal Antibodies: Principles and Practice (2d ed.), Academic Press, New York; and particularly in Kohler and Milstein (1975) in Nature 256:495-497, which discusses one method of generating monoclonal antibodies.

Other suitable techniques involve in vitro exposure of lymphocytes to the antigenic polypeptides or alternatively to selection of libraries of antibodies in phage or similar vectors. See, Huse, et al. (1989) "Generation of a Large Combinatorial Library of the Immunoglobulin Repertoire in Phage Lambda," Science 246:1275-1281; and Ward, et al. (1989) Nature 341:544-546. The polypeptides and antibodies of the present invention may be used

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with or without modification, including chimeric or humanized antibodies. Frequently, the polypeptides and antibodies will be labeled by joining, either covalently or non-covalently, a substance which provides for a detectable signal. A wide variety of labels and conjugation techniques are known and are reported extensively in both the scientific and patent literature. Suitable labels include radionuclides, enzymes, substrates, cofactors, inhibitors, fluorescent moieties, chemiluminescent moieties, magnetic particles, and the like. Patents, teaching the use of such labels include U.S. Patent Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241. Also, recombinant immunoglobulins may be produced, see Cabilly, U.S. Patent No. 4,816,567; Moore, et al., U.S. Patent No. 4,642,334; and Queen, et al. (1989) Proc. Nat'l Acad. Sci. USA 86:10029-10033.

The antibodies of this invention can also be used for affinity chromatography in isolating the protein. Columns can be prepared where the antibodies are linked to a solid support, e.g., particles, such as agarose, Sephadex, or the like, where a cell lysate may be passed through the column, the column washed, followed by increasing concentrations of a mild denaturant, whereby the purified protein will be released. See, e.g., Wilchek et al. (1984) Meth. Enzymol. 104:3-55.

Antibodies raised against each protein will also be useful to raise anti-idiotypic antibodies. These will be useful in detecting or diagnosing various immunological conditions related to expression of the respective antigens.

VI. Nucleic Acids

The described peptide sequences and the related reagents are useful in detecting, isolating, or identifying a DNA clone encoding, e.g., the DC-PGT, HDTEA84, HSLJD37R, RANKL, HCC5, Dub11, Dub12, MD-1, MD-2, or cyclin E2 polypeptides, e.g., from a natural source. Typically, the nucleic acids, particularly natural genes, will be useful in isolating a gene from mammal, and similar procedures will be applied to isolate genes from other species, e.g., warm blooded animals, such as birds and mammals. They will

be useful for isolating genes from domestic pets, e.g., dogs and cats, and livestock, e.g., horse, pigs, cattle, sheep, chickens, turkeys, fish, etc. Cross hybridization will allow isolation of respective counterpart genes from other species. A number of
5 different approaches should be available to successfully isolate a suitable nucleic acid clone.

The peptide sequences allow preparation of peptides to generate antibodies to recognize such segments, and various different methods may be used to prepare such peptides. As used
10 herein, e.g., the term prostaglandin transporter shall encompass, when used in a protein context, a protein having an amino acid sequence shown in Table 1, or a significant fragment of such a protein. It also refers to a vertebrate, e.g., mammal, including human, derived polypeptide which exhibits similar biological
15 function, e.g., antigenic, or interacts with prostaglandin transporter specific binding components, e.g., specific antibodies. These binding components, e.g., antibodies, typically bind to a prostaglandin transporter with high affinity, e.g., at least about 100 nM, usually better than about 30 nM, preferably
20 better than about 10 nM, and more preferably at better than about 3 nM. Still higher affinities are possible, e.g., 100 pM, 30 pM, 100 fM, etc.

This invention contemplates use of isolated DNA or fragments of the present invention to encode a structurally related, e.g.,
25 antigenically related, or biologically active protein, e.g., substrate binding or transporting, prostaglandin transporter, TNF receptor-like proteins, chemokine, Dubs, surface receptors, or cell cycle regulatory proteins, or polypeptide fragments thereof. In addition, this invention covers isolated or recombinant DNA
30 which encodes a structurally related or biologically active protein or polypeptide and that is capable of hybridizing under appropriate conditions with the DNA sequences described herein. Said biologically active protein or polypeptide can be an intact antigen, or fragment, and have an amino acid sequence as disclosed
35 in Tables 1-13. Further, this invention covers the use of isolated or recombinant DNA, or fragments thereof, which encode proteins which are homologous to the respective genes or which

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were isolated using cDNA encoding the proteins as a probe. Preferably such homologous genes or proteins will be natural forms isolated from other vertebrates, e.g., warm blooded animals, including mammals, such as primates. The isolated DNA can have the respective regulatory sequences in the 5' and 3' flanks, e.g., promoters, enhancers, poly-A addition signals, and others.

An "isolated" nucleic acid is a nucleic acid, e.g., an RNA, DNA, or a mixed polymer, which is substantially separated from other components which naturally accompany a native sequence, e.g., ribosomes, polymerases, and flanking genomic sequences from the originating species. The term embraces a nucleic acid sequence which has been removed from its naturally occurring intracellular environment, and includes recombinant or cloned DNA isolates and chemically synthesized analogs or analogs biologically synthesized by heterologous systems. A substantially pure molecule includes once or currently isolated forms of the molecule. Alternatively, a purified species may be separated from host components from a recombinant expression system. Generally, the nucleic acid will be in a vector or fragment less than about 50 kb, usually less than about 30 kb, typically less than about 10 kb, and preferably less than about 6 kb.

An isolated nucleic acid will generally be a homogeneous composition of molecules, but will, in some embodiments, contain minor heterogeneity. This heterogeneity is typically found at the polymer ends or portions not critical to a desired biological function or activity.

The peptide segments can also be used to predict appropriate oligonucleotides to screen a library. The genetic code, e.g., reverse translation, can be used to select appropriate oligonucleotides useful as probes for screening. See, e.g., SEQ ID NO: 1, 5, 7, 9, 11, 16, 18, 20, 22, 24, 31, 33, 35, 37, 41, 43, 47, or 53. In combination with polymerase chain reaction (PCR) techniques, synthetic oligonucleotides will be useful in selecting correct clones from a library. Complementary sequences will also be used as probes, primers, or antisense strands. Various fragments should be particularly useful, e.g., coupled with

anchored vector or poly-A complementary PCR techniques or with complementary DNA of other peptides.

This invention contemplates use of isolated DNA or fragments to encode a biologically active corresponding polypeptide. In addition, this invention covers isolated or recombinant DNA which encodes a biologically active protein or polypeptide which is capable of hybridizing under appropriate conditions with the DNA sequences described herein. Said biologically active protein or polypeptide can be an intact antigen, or fragment, and have an amino acid sequence disclosed in, e.g., SEQ ID NO: 2, 6, 8, 10, 12, 17, 19, 21, 23, 25, 32, 34, 36, 38, 42, 44, 46, 48, 49, or 54. Further, this invention covers the use of isolated or recombinant DNA, or fragments thereof, which encode proteins which are homologous to a described protein or which was isolated using cDNA encoding such protein as a probe. The isolated DNA can have the respective regulatory sequences in the 5' and 3' flanks; e.g., promoters, enhancers, poly-A addition signals, and others.

A "recombinant" nucleic acid is defined either by its method of production or its structure. In reference to its method of production, e.g., a product made by a process, the process is use of recombinant nucleic acid techniques, e.g., involving human intervention in the nucleotide sequence, typically selection or production. Alternatively, it can be a nucleic acid made by generating a sequence comprising fusion of two fragments which are not naturally contiguous to each other, but is meant to exclude products of nature, e.g., naturally occurring mutants. Thus, e.g., products made by transforming cells with any unnaturally occurring vector is encompassed, as are nucleic acids comprising sequence derived using any synthetic oligonucleotide process. Such is often done to replace a codon with a redundant codon encoding the same or a conservative amino acid, while typically introducing or removing a sequence recognition site.

Alternatively, it is performed to join together nucleic acid segments of desired functions to generate a single genetic entity comprising a desired combination of functions not found in the commonly available natural forms. Restriction enzyme recognition sites are often the target of such artificial manipulations, but

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other site specific targets, e.g., promoters, DNA replication sites, regulation sequences, control sequences, or other useful features may be incorporated by design. A similar concept is intended for a recombinant, e.g., fusion, polypeptide.

- 5 Specifically included are synthetic nucleic acids which, by genetic code redundancy, encode polypeptides similar to fragments of these antigens, and fusions of sequences from various different species variants.

- 10 A significant "fragment" in a nucleic acid context is a contiguous segment of at least about 17 nucleotides, generally at least about 22 nucleotides, ordinarily at least about 29 nucleotides, more often at least about 35 nucleotides, typically at least about 41 nucleotides, usually at least about 47 nucleotides, preferably at least about 55 nucleotides, and in
15 particularly preferred embodiments will be at least about 60 or more nucleotides.

- A DNA which codes for a DC-PGT, HDTEA84, HSLJD37R, RANKL, HCC5, Dub, MD-1, MD-2, or cyclin E2 protein will be particularly useful to identify genes, mRNA, and cDNA species which code for
20 related or homologous proteins, as well as DNAs which code for homologous proteins from different species. There are likely homologs in other species, including primates, rodents, birds, and fish. Various such proteins should be homologous and are encompassed herein. However, even genes encoding proteins that
25 have a more distant evolutionary relationship to the antigen can readily be isolated under appropriate conditions using these sequences if they are sufficiently homologous. Primate proteins are of particular interest.

- Recombinant clones derived from the genomic sequences, e.g.,
30 containing introns, will be useful for transgenic studies, including, e.g., transgenic cells and organisms, and for gene therapy. See, e.g., Goodnow (1992) "Transgenic Animals" in Roitt (ed.) Encyclopedia of Immunology, Academic Press, San Diego, pp. 1502-1504; Travis (1992) Science 256:1392-1394; Kuhn, et al.
35 (1991) Science 254:707-710; Capecchi (1989) Science 244:1288; Robertson (1987 ed.) Teratocarcinomas and Embryonic Stem Cells: A

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Practical Approach, IRL Press, Oxford; and Rosenberg (1992) J. Clinical Oncology 10:180-199.

Substantial homology in the nucleic acid sequence comparison context means either that the segments, or their complementary strands, when compared, are identical when optimally aligned, with appropriate nucleotide insertions or deletions, in at least about 50% of the nucleotides, generally at least about 58%, ordinarily at least about 65%, often at least about 71%, typically at least about 77%, usually at least about 85%, preferably at least about 95 to 98% or more, and in particular embodiments, as high as about 99% or more of the nucleotides. Alternatively, substantial homology exists when the segments will hybridize under selective hybridization conditions, to a strand, or its complement, typically using a sequence of DC-PGT, e.g., in SEQ ID NO: 1.

Typically, selective hybridization will occur when there is at least about 55% homology over a stretch of at least about 30 nucleotides, preferably at least about 75% over a stretch of about 25 nucleotides, and most preferably at least about 90% over about 20 nucleotides. See, Kanehisa (1984) Nuc. Acids Res. 12:203-213.

The length of homology comparison, as described, may be over longer stretches, and in certain embodiments will be over a stretch of at least about 17 nucleotides, usually at least about 28 nucleotides, typically at least about 40 nucleotides, and preferably at least about 75 to 100 or more nucleotides.

Stringent conditions, in referring to homology in the hybridization context, will be stringent combined conditions of salt, temperature, organic solvents, and other parameters, typically those controlled in hybridization reactions. Stringent temperature conditions will usually include temperatures in excess of about 30° C, usually in excess of about 37° C, typically in excess of about 55° C, preferably in excess of about 70° C. Stringent salt conditions will ordinarily be less than about 1000 mM, usually less than about 400 mM, typically less than about 250 mM, preferably less than about 150 mM. However, the combination of parameters is much more important than the measure of any single parameter. See, e.g., Wetmur and Davidson (1968) J. Mol. Biol. 31:349-370. Hybridization under stringent conditions should

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give a background of at least 2-fold over background, preferably at least 3-5 or more.

DC-PGT, HDTEA84, HSLJD37R, RANKL, HCC5, Dub11, Dub12, MD-1, MD-2, or cyclin E2 from other mammalian species can be cloned and
5 isolated by cross-species hybridization of closely related species. Homology may be relatively low between distantly related species, and thus hybridization of relatively closely related species is advisable. Alternatively, preparation of an antibody
preparation which exhibits less species specificity may be useful
10 in expression cloning approaches.

VII. Making Proteins; Mimetics

Nucleic acids which encodes the described proteins, or fragments thereof, can be obtained by chemical synthesis,
15 screening cDNA libraries, or screening genomic libraries prepared from a wide variety of cell lines or tissue samples. See, e.g., Okayama and Berg (1982) Mol. Cell. Biol. 2:161-170; Gubler and Hoffman (1983) Gene 25:263-269; and Glover (ed. 1984) DNA Cloning: A Practical Approach, IRL Press, Oxford. Alternatively, the
20 sequences provided herein provide useful PCR primers or allow synthetic or other preparation of suitable genes encoding a receptor; including, naturally occurring embodiments.

DNA can be expressed in a wide variety of host cells for the synthesis of a full-length protein, or fragments, which can in
25 turn, e.g., be used to generate polyclonal or monoclonal antibodies; for binding studies; for construction and expression of modified molecules; for structure/function studies; and for controls in detection assays. Each antigen or its fragments can be expressed in host cells that are transformed or transfected.
30 with appropriate expression vectors. These molecules can be substantially purified to be free of protein or cellular contaminants, other than those derived from the recombinant host, and therefore are particularly useful in pharmaceutical compositions when combined with a pharmaceutically acceptable
35 carrier and/or diluent. The antigen, or portions thereof, may be expressed as fusions with other proteins.

Vectors, as used herein, comprise plasmids, viruses, bacteriophage, integratable DNA fragments, and other vehicles which enable the integration of DNA fragments into the genome of the host. See, e.g., Pouwels, et al. (1985 and Supplements)

5 Cloning Vectors: A Laboratory Manual, Elsevier, N.Y.; and Rodriguez, et al. (1988 eds.) Vectors: A Survey of Molecular Cloning Vectors and Their Uses, Buttersworth, Boston, MA.

Expression vectors are typically self-replicating DNA or RNA constructs containing the desired antigen gene or its fragments, usually operably linked to suitable genetic control elements that are recognized in a suitable host cell. These control elements are capable of effecting expression within a suitable host. The specific type of control elements necessary to effect expression will depend upon the eventual host cell used. Generally, the genetic control elements can include a prokaryotic promoter system or a eukaryotic promoter expression control system, and typically include a transcriptional promoter, an optional operator to control the onset of transcription, transcription enhancers to elevate the level of mRNA expression, a sequence that encodes a suitable ribosome binding site, and sequences that terminate transcription and translation. Expression vectors also usually contain an origin of replication that allows the vector to replicate independently of the host cell.

For purposes of this invention, DNA sequences are operably linked when they are functionally related to each other. For example, DNA for a presequence or secretory leader is operably linked to a polypeptide if it is expressed as a preprotein or participates in directing the polypeptide to the cell membrane or in secretion of the polypeptide. A promoter is operably linked to a coding sequence if it controls the transcription of the polypeptide; a ribosome binding site is operably linked to a coding sequence if it is positioned to permit translation. Usually, operably linked means contiguous and in reading frame, however, certain genetic elements such as repressor genes are not contiguously linked but still bind to operator sequences that in turn control expression. See e.g., Rodriguez, et al., Chapter 10, pp. 205-236; Balbas and Bolivar (1990) Methods in Enzymol. 185:14-

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37; and Ausubel, et al. (1993) Current Protocols in Molecular Biology, Greene and Wiley, NY.

Representative examples of suitable expression vectors include pCDNA1; pCD, see Okayama, et al. (1985) Mol. Cell Biol. 5:1136-1142; pMC1neo Poly-A, see Thomas, et al. (1987) Cell 51:503-512; and a baculovirus vector such as pAC 373 or pAC 610. See, e.g., Miller (1988) Ann. Rev. Microbiol. 42:177-199.

Usually, expression vectors are designed for stable replication in their host cells or for amplification to greatly increase the total number of copies of the desirable gene per cell. It is not always necessary to require that an expression vector replicate in a host cell, e.g., it is possible to effect transient expression of the antigen or its fragments in various hosts using vectors that do not contain a replication origin that is recognized by the host cell. It is also possible to use vectors that cause integration of a gene or its fragments into the host DNA by recombination, or to integrate a promoter which controls expression of an endogenous gene.

Adenovirus techniques are available for expression of the genes in various cells and organs. See, e.g., Hitt, et al. (1997) Adv. Pharmacol. 40:137-195; and literature from Quantum Biotechnologies, Montreal, Canada. Animals may be useful to determine the effects of the gene on various developmental or physiologically functional animal systems.

Suitable host cells include prokaryotes, lower eukaryotes, and higher eukaryotes. Prokaryotes include both gram negative and gram positive organisms, e.g., *E. coli* and *B. subtilis*. Lower eukaryotes include yeasts, e.g., *S. cerevisiae* and *Pichia*, and species of the genus *Dictyostelium*. Higher eukaryotes include established tissue culture cell lines from animal cells, both of non-mammalian origin, e.g., insect cells, and birds, and of mammalian origin, e.g., human, primates, and rodents.

Prokaryotic host-vector systems include a wide variety of vectors for many different species. As used herein, *E. coli* and its vectors will be used generically to include equivalent vectors used in other prokaryotes. A representative vector for amplifying DNA is pBR322 or many of its derivatives. Vectors that can be

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used to express the prostaglandin transporter or its fragments include, but are not limited to, such vectors as those containing the lac promoter (pUC-series); trp promoter (pBR322-trp); Ipp promoter (the pIN-series); lambda-pP or pR promoters (pOTS); or hybrid promoters such as ptac (pDR540). See Brosius et al. (1988) "Expression Vectors Employing Lambda-, trp-, lac-, and Ipp-derived Promoters", in Rodriguez and Denhardt (eds.) Vectors: A Survey of Molecular Cloning Vectors and Their Uses, Butterworth, Boston, Chapter 10, pp. 205-236, which is incorporated herein by reference.

Lower eukaryotes, e.g., yeasts and Dictyostelium, may be transformed with vectors encoding vertebrate prostaglandin transporters. For purposes of this invention, the most common lower eukaryotic host is the baker's yeast, Saccharomyces cerevisiae. It will be used to generically represent lower eukaryotes although a number of other strains and species are also available. Yeast vectors typically consist of a replication origin (unless of the integrating type), a selection gene, a promoter, DNA encoding the desired protein or its fragments, and sequences for translation termination, polyadenylation, and transcription termination. Suitable expression vectors for yeast include such constitutive promoters as 3-phosphoglycerate kinase and various other glycolytic enzyme gene promoters or such inducible promoters as the alcohol dehydrogenase 2 promoter or metallothionine promoter. Suitable vectors include derivatives of the following types: self-replicating low copy number (such as the YRp-series), self-replicating high copy number (such as the YEpl-series); integrating types (such as the YIp-series), or mini-chromosomes (such as the YCp-series).

Higher eukaryotic tissue culture cells are the preferred host cells for expression of the functionally active prostaglandin transporter. In principle, most higher eukaryotic tissue culture cell lines are workable, e.g., insect baculovirus expression systems, whether from an invertebrate or vertebrate source. However, mammalian cells are preferred, in that the processing, both cotranslationally and posttranslationally is more likely to simulate natural forms. Transformation or transfection and

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propagation of such cells has become a routine procedure.

Examples of useful cell lines include HeLa cells, Chinese hamster ovary (CHO) cell lines, baby rat kidney (BRK) cell lines, insect cell lines, bird cell lines, and monkey (COS) cell lines.

- 5 Expression vectors for such cell lines usually include an origin of replication, a promoter, a translation initiation site, RNA splice sites (if genomic DNA is used), a polyadenylation site, and a transcription termination site. These vectors also usually contain a selection gene or amplification gene. Suitable
10 expression vectors may be plasmids, viruses, or retroviruses carrying promoters derived, e.g., from such sources as from adenovirus, SV40, parvoviruses, vaccinia virus, or cytomegalovirus. Representative examples of suitable expression vectors include pCDNA1; pCD, see Okayama et al. (1985) Mol. Cell Biol. 5:1136-1142; pMC1neo Poly-A, see Thomas et al. (1987) Cell 51:503-512; and a baculovirus vector such as pAC 373 or pAC 610.

- It will often be desired to express a DC-PGT, HDTEA84, HSLJD37R, RANKL, HCC5, Dub11, Dub12, MD-1, MD-2, or cyclin E2 polypeptide in a system which provides a specific or defined
20 glycosylation pattern. See, e.g., Luckow and Summers (1988) Bio/Technology 6:47-55; and Kaufman (1990) Meth. Enzymol. 185:487-511. Preferred prokaryotic forms lack eukaryotic glycosylation patterns. However, the pattern will be modifiable by exposing the polypeptide, e.g., an unglycosylated form, to appropriate
25 glycosylating proteins introduced into a heterologous expression system. For example, the desired gene may be cotransformed with one or more genes encoding mammalian or other glycosylating enzymes. Using this approach, certain mammalian glycosylation patterns will be achievable or approximated in prokaryote or other
30 cells.

- The DC-PGT, HDTEA84, HSLJD37R, RANKL, HCC5, Dub11, Dub12, MD-1, MD-2, or cyclin E2, or a fragment thereof, may be engineered to be phosphatidyl inositol (PI) linked to a cell membrane, but can be removed from membranes by treatment with a phosphatidyl
35 inositol cleaving enzyme, e.g., phosphatidyl inositol phospholipase-C. This releases the antigen in a biologically active form, and allows purification by standard procedures of

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protein chemistry. See, e.g., Low (1989) Biochim. Biophys. Acta 988:427-454; Tse, et al. (1985) Science 230:1003-1008; and Brunner, et al. (1991) J. Cell Biol. 114:1275-1283.

Transformed cells include cells, preferably mammalian, that have been transformed or transfected with vectors containing a prostaglandin transporter gene, typically constructed using recombinant DNA techniques. Transformed host cells usually express the antigen or its fragments, but for purposes of cloning, amplifying, and manipulating its DNA, do not need to express the protein. This invention further contemplates culturing transformed cells in a nutrient medium, thus permitting the protein, or soluble fragments, to accumulate in the culture. Soluble protein can be recovered, either from the culture or from the culture medium, and membrane associated proteins may be prepared from suitable cell subfractions.

Now that the genes have been characterized, fragments or derivatives thereof can be prepared by conventional processes for synthesizing peptides. These include processes such as are described in Stewart and Young (1984) Solid Phase Peptide Synthesis, Pierce Chemical Co., Rockford, IL; Bodanszky and Bodanszky (1984) The Practice of Peptide Synthesis, Springer-Verlag, New York; and Bodanszky (1984) The Principles of Peptide Synthesis, Springer-Verlag, New York. For example, an azide process, an acid chloride process, an acid anhydride process, a mixed anhydride process, an active ester process (for example, p-nitrophenyl ester, N-hydroxysuccinimide ester, or cyanomethyl ester), a carbodiimidazole process, an oxidative-reductive process, or a dicyclohexylcarbodiimide (DCCD)/additive process can be used. Solid phase and solution phase syntheses are both applicable to the foregoing processes.

The proteins, fragments, or derivatives are suitably prepared in accordance with the above processes as typically employed in peptide synthesis, generally either by a so-called stepwise process which comprises condensing an amino acid to the terminal amino acid, one by one in sequence, or by coupling peptide fragments to the terminal amino acid. Amino groups that are not

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being used in the coupling reaction are typically protected to prevent coupling at an incorrect location.

If a solid phase synthesis is adopted, the C-terminal amino acid is bound to an insoluble carrier or support through its carboxyl group. The insoluble carrier is not particularly limited as long as it has a binding capability to a reactive carboxyl group. Examples of such insoluble carriers include halomethyl resins, such as chloromethyl resin or bromomethyl resin, hydroxymethyl resins, phenol resins, tert-alkyloxycarbonyl-hydrazidated resins, and the like.

An amino group-protected amino acid is bound in sequence through condensation of its activated carboxyl group and the reactive amino group of the previously formed peptide or chain, to synthesize the peptide step by step. After synthesizing the complete sequence, the peptide is split off from the insoluble carrier to produce the peptide. This solid-phase approach is generally described by Merrifield et al. (1963) in J. Am. Chem. Soc. 85:2149-2156, which is incorporated herein by reference.

The prepared protein and fragments thereof can be isolated and purified from the reaction mixture by means of peptide separation, e.g., by extraction, precipitation, electrophoresis and various forms of chromatography, and the like. The proteins of this invention can be obtained in varying degrees of purity depending upon its desired use. Purification can be accomplished by use of the protein purification techniques disclosed herein or by the use of the antibodies herein described in immunoabsorbent affinity chromatography. This immunoabsorbent affinity chromatography is carried out by first linking the antibodies to a solid support and then contacting the linked antibodies with solubilized lysates of appropriate source cells, lysates of other cells expressing the protein, or lysates or supernatants of cells producing the desired protein as a result of DNA techniques, see below. Detergents may be necessary to include in the methods to maintain protein solubility.

VIII. Uses

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The present invention provides reagents which will find use in diagnostic applications as described elsewhere herein, e.g., in the general description for cell mediated conditions, or below in the description of kits for diagnosis. The genes will be useful in forensic analyses, e.g., to identify species, or to diagnose different cell subsets or types.

If DC-PGT is used to clear prostaglandins (PGs) and other metabolically active organic anions from the body (in the liver, fetal liver, lung and placenta) it is easy to suppose that an alteration in the capacity of this mechanism could augment the allergic response. Prostaglandin $\text{PGF}_2\alpha$ and PGD_2 , and PGG_2 and thromboxane A_2 can cause airway obstruction, particularly in the peripheral lung, while PGE_2 and PGI_2 are bronchodilators. Use of the transporter of the invention could help transport or remove these prostaglandins to modulate airway obstruction.

Additionally, prostaglandins play an important role in secondary immunosuppression seen following surgical stress. Alexander (1990) J. Trauma 30:S70; Faist, et al. (1987) J. Trauma 27:837; Ninneman, et al. (1984) J. Trauma 24:201; Wood, et al. (1987) Arch. Surg. 122:179; Polk, et al. in Eremin and Sewell (eds. 1992) The Immunological Basis of Surgical Science and Practice, Oxford U. Press. In particular, PGE_2 inhibits lymphocyte proliferation, decreases IL-2 release, decreases response to IL-2, inhibits natural killer cells, and activates suppressor cells. Major injury has been shown to result in increased production of PGE_2 from inhibitory macrophages, with a resulting decrease in production of IL-1 and IL-2. This effect may persist for 7 to 10 days after major injury. Other studies have shown no increase in circulating PGE_2 following burns but did find increased local production with increased sensitivity of lymphocytes to the action of PGE_2 .

Prostaglandin E_2 , through locally produced vasodilatory effects, may play a role in rheumatoid arthritis by promoting the entry of inflammatory cells into the joint. Once in the synovial fluid, polymorphonuclear leukocytes can ingest immune complexes, which, in turn, cause neutrophils to produce reactive oxygen

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metabolites and other inflammatory mediators to further enhance an inflammatory cascade. Henson, et al. (1987) J. Clin. Invest. 79:699.

Accordingly, it is possible to use the present invention to
5 modulate prostaglandins in a subject suffering from trauma, injury, disease or in post-surgical treatments:

Immune system cells may be synthesizing PGs and thus using DC-PGT in an efflux role for removing PGs from the intracellular space may be useful. Equally, DC-PGT might transport a specific
10 organic anion. Abnormal proliferation, regeneration, degeneration, and atrophy may be modulated by appropriate therapeutic treatment using the compositions provided herein. For example, a disease or disorder associated with abnormal function of a prostaglandin transporter should be a likely target for a
15 substrate or blocking substrate. Alternatively, the transporter may be a useful means for supplying important metabolites or metabolite blockers to the respective cells.

For example, transformation with the transporter may increase availability of the substrate to the cell. In certain situations,
20 a prostaglandin analog might be advantageously supplied to the cell. The prostaglandin analog might confer high susceptibility to further treatment, e.g., radiation sensitivity or otherwise, or may directly affect normal metabolism, e.g., nucleic acid related enzymes. Alternatively, the transporter may be useful to screen
25 for antagonists or inhibitors, which might be effective in blocking the normal availability to the cell of the natural substrate. Screening methods for such prostaglandin analogs are provided.

Screening using prostaglandin transporter for binding
30 metabolites or compounds having binding affinity to the transporter can be performed, including isolation of associated components. Subsequent biological assays can then be utilized to determine if the compound has intrinsic biological activity and is therefore an agonist or antagonist in that it blocks an activity
35 of the transporter. In particular, prostaglandin analogs may be useful in blocking binding of the natural target or otherwise blocking transporter activity. Alternatively, various other

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analogs may be useful in blocking an ion transporter, or organic anion source. This invention further contemplates the therapeutic use of antibodies to prostaglandin transporter as antagonists. This approach should be particularly useful with other
5 prostaglandin transporter species variants and other members of the family.

Antagonists of the transporter activity, e.g., antibodies which block the transport, may be useful in various medical conditions. These would include immune, inflammatory or allergic
10 abnormalities, all of which are important where transfer of organic anions take place. Certain congenital diseases of prostaglandin physiology will be susceptible to such a therapeutic approach.

The HDTEA84, HSLJD37R, RANKL, HCC5, MD-1, or MD-2 (naturally
15 occurring or recombinant), fragments thereof, and antibodies thereto, along with compounds identified as having binding affinity to them, should be useful in the treatment of conditions associated with abnormal physiology or development, including abnormal proliferation, e.g., cancerous conditions, or
20 degenerative conditions. In particular, modulation of development of lymphoid cells will be achieved by appropriate therapeutic treatment using the compositions provided herein. For example, a disease or disorder associated with abnormal expression or abnormal signaling by a ligand or receptor should be a likely
25 target for an agonist or antagonist of the antigen. The antigen plays a role in regulation or development of hematopoietic cells, e.g., lymphoid cells, which affect immunological responses, e.g., autoimmune disorders.

In particular, the antigen may provide a costimulatory signal
30 to cell activation, or be involved in regulation of cell proliferation or differentiation. Thus, the HDTEA84, HSLJD37R, RANKL, HCC5, MD-1, or MD-2 will likely modulate cells which possess a receptor therefor, e.g., T cell mediated interactions with other cell types. These interactions would lead, in
35 particular contexts, to modulation of cell growth, cytokine synthesis by those or other cells, or development of particular effector cells.

Moreover, the HDTEA84, HSLJD37R, RANKL, HCC5, MD-1, or MD-2 or antagonists could redirect T cell responses, e.g., between Th1 and Th2 polarization, or with Th0 cells, or may affect B cells or other lymphoid cell subsets. Among these agonists should be various antibodies which recognize the appropriate epitopes, e.g., which mimic binding of ligand or receptor to its partner. Alternatively, they may bind to epitopes which sterically can block receptor binding. Bone morphogenesis may be regulated by these receptor segments.

The ligands or receptors may provide a selective and powerful way to modulate immune responses in abnormal situations, e.g., autoimmune disorders, including rheumatoid arthritis, systemic lupus erythematosus (SLE), Hashimoto's autoimmune thyroiditis, as well as acute and chronic inflammatory responses in which T cell activation, expansion, and/or immunological T cell memory play an important role. See also Samter, et al. (eds) Immunological Diseases vols. 1 and 2, Little, Brown and Co. Regulation of bone morphogenesis, T cell activation, expansion, and/or cytokine release by the naturally occurring secreted form of HDTEA84, HSLJD37R, RANKL, HCC5, MD-1, or MD-2, or an antagonist thereof, may be effected.

In addition, certain combination compositions with other modulators of signaling would be useful, especially with the TNF receptor-like genes. Such other signaling molecules might include, e.g., TCR reagents, CD40, CD40L, CTLA-8, CD28, SLAM, FAS, osteoprotegerin, and their respective antagonists, including antibodies.

Cyclin E2 nucleotides, e.g., human cyclin E2 DNA or RNA, may be used as a component in a forensic assay. For instance, the nucleotide sequences provided may be labeled using, e.g., ³²P or biotin and used to probe standard restriction fragment polymorphism blots, providing a measurable character to aid in distinguishing between individuals. Such probes may be used in well-known forensic techniques such as genetic fingerprinting. In addition, nucleotide probes made from cyclin E2 sequences may be used in in situ assays to detect chromosomal abnormalities. For instance, rearrangements in the human chromosome encoding a cyclin

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E2 gene may be detected via well-known in situ techniques, using cyclin E2 probes in conjunction with other known chromosome markers. The cyclin E2 gene may have useful prognostic utility in various cancers, e.g., breast, etc.

5 Antibodies and other binding agents directed towards cyclin E2 proteins or nucleic acids may be used to purify the corresponding cyclin E2 molecule. As described in the Examples below, antibody purification of cyclin E2 protein components is both possible and practicable. Antibodies and other binding
10 agents may also be used in a diagnostic fashion to determine whether cyclin E2 protein components are present in a tissue sample or cell population using well-known techniques described herein. The ability to attach a binding agent to a cyclin E2 protein provides a means to diagnose disorders associated with
15 cyclin E2 protein misregulation. Antibodies and other cyclin E2 protein binding agents may also be useful as histological markers. As described in the examples below, cyclin E2 protein expression is limited to specific tissue types. By directing a probe, such as an antibody or nucleic acid to a cyclin E2 protein it is
20 possible to use the probe to distinguish tissue and cell types in situ or in vitro.

 This invention also provides reagents with significant therapeutic value. The cyclin E2 protein (naturally occurring or recombinant), fragments thereof, and antibodies thereto, along
25 with compounds identified as having binding affinity to a cyclin E2 protein, can be useful in the treatment of conditions associated with abnormal physiology or development, including abnormal proliferation, e.g., cancerous conditions, or degenerative conditions. Abnormal proliferation, regeneration,
30 degeneration, and atrophy may be modulated by appropriate therapeutic treatment using the compositions provided herein. For example, a disease or disorder associated with abnormal expression or abnormal signaling by a cyclin E2 protein is a target for an agonist or antagonist of the protein. The proteins likely play a
35 role in regulation or development of neuronal or hematopoietic cells, e.g., lymphoid cells, which affect immunological responses.

Various abnormal conditions are known in each of the cell types shown to possess, e.g., HDTEA84, mRNA by Northern blot analysis. See Berkow (ed.) The Merck Manual of Diagnosis and Therapy, Merck & Co., Rahway, NJ; Thorn, et al. Harrison's Principles of Internal Medicine, McGraw-Hill, NY; and Weatherall, et al. (eds.) Oxford Textbook of Medicine, Oxford University Press, Oxford. Many other medical conditions and diseases involve T cells or are T cell mediated, and many of these may be responsive to treatment by an agonist or antagonist provided herein. See, e.g., Stites and Terr (eds; 1991) Basic and Clinical Immunology Appleton and Lange, Norwalk, CT; and Samter, et al. (eds) Immunological Diseases Little, Brown and Co. These problems should be susceptible to prevention or treatment using compositions provided herein.

Specific, or selective, antibodies can be purified and then administered to a patient, veterinary or human. These reagents can be combined for therapeutic use with additional active or inert ingredients, e.g., in conventional pharmaceutically acceptable carriers or diluents, e.g., immunogenic adjuvants, along with physiologically innocuous stabilizers, excipients, or preservatives. These combinations can be sterile filtered and placed into dosage forms as by lyophilization in dosage vials or storage in stabilized aqueous preparations. This invention also contemplates use of antibodies or binding fragments thereof, including forms which are not complement binding.

Drug screening using proteins or fragments thereof can be performed to identify compounds having binding affinity to or other relevant biological effects on antigen functions, including isolation of associated components. Subsequent biological assays can then be utilized to determine if the compound has intrinsic stimulating activity or is a blocker or antagonist in that it blocks the activity of the antigen, e.g., mutein antagonists. Likewise, a compound having intrinsic stimulating activity can activate the signal pathway and is thus an agonist in that it overcomes any blocking activity of these soluble forms of receptors. This invention further contemplates the therapeutic use of blocking antibodies to ligands or receptors as agonists or

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antagonists and of stimulatory molecules, e.g., muteins, as agonists. This approach should be particularly useful with other soluble receptor species variants.

Another therapeutic approach included within the invention
5 involves direct administration of reagents or compositions by any conventional administration techniques (e.g., but not restricted to local injection, inhalation, or administered systemically), to the subject with an immune, allergic, or trauma disorder. The reagents, formulations, or compositions included within the bounds
10 and metes of the invention may also be targeted to specific cells or transporters by methods described herein. The actual dosage of reagent, formulation, or composition that modulates an immune, allergic, or trauma disorder depends on many factors, including the size and health of an organism, however one of ordinary skill
15 in the art can use the following teachings describing the methods and techniques for determining clinical dosages. See, e.g., Spilker (1984) Guide to Clinical Studies and Developing Protocols, Raven Press Books, Ltd., New York, pp. 7-13, 54-60; Spilker (1991) Guide to Clinical Trials, Raven Press, Ltd., New York, pp. 93-101;
20 Craig and Stitzel (eds. 1986) Modern Pharmacology, 2d ed., Little, Brown and Co., Boston, pp. 127-33; Speight (ed. 1987) Avery's Drug Treatment: Principles and Practice of Clinical Pharmacology and Therapeutics, 3d ed., Williams and Wilkins, Baltimore, pp. 50-56;
Tallarida, et al. (1988) Principles in General Pharmacology,
25 Springer-Verlag, New York, pp. 18-20). Generally, the dose will be in the range of about between 0.5 fg/ml and 500 µg/ml, inclusive, final concentration administered per day to an adult in a pharmaceutically acceptable carrier.

The quantities of reagents necessary for effective therapy
30 will depend upon many different factors, including means of administration, target site, physiological state of the patient, and other medicants administered. Thus, treatment dosages should be titrated to optimize safety and efficacy. Typically, dosages used in vitro may provide useful guidance in the amounts useful
35 for in situ administration of these reagents. Animal testing of effective doses for treatment of particular disorders will provide

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further predictive indication of human dosage. Various considerations are described, e.g., in Gilman, et al. (eds. 1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics, 8th Ed., Pergamon Press; and Remington's Pharmaceutical Sciences, 17th ed. (1990), Mack Publishing Co., Easton, Penn. Methods for administration are discussed, e.g., for oral, intravenous, intraperitoneal, or intramuscular administration, transdermal diffusion, and others. Pharmaceutically acceptable carriers will include water, saline, buffers, and other compounds described, e.g., in the Merck Index, Merck & Co., Rahway, New Jersey. Dosage ranges would ordinarily be expected to be in amounts lower than 1 mM concentrations, typically less than about 10 μ M concentrations, usually less than about 100 nM, preferably less than about 10 pM (picomolar), and most preferably less than about 1 fM (femtomolar), with an appropriate carrier. Slow release formulations, or a slow release apparatus will often be utilized for continuous or long term administration. See, e.g., Langer (1990) Science 249:1527-1533.

Ligands, receptors, enzymes, fragments thereof, and antibodies to it or its fragments, antagonists, and agonists, may be administered directly to the host to be treated or, depending on the size of the compounds, it may be desirable to conjugate them to carrier proteins such as ovalbumin or serum albumin prior to their administration. Therapeutic formulations may be administered in many conventional dosage formulations. While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical formulation. Formulations typically comprise at least one active ingredient, as defined above, together with one or more acceptable carriers thereof. Each carrier should be both pharmaceutically and physiologically acceptable in the sense of being compatible with the other ingredients and not injurious to the patient. Formulations include those suitable for oral, rectal, nasal, topical, or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by methods well known in the art of pharmacy. See, e.g., Gilman,

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et al. (eds. 1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics, 8th Ed., Pergamon Press; and Remington's Pharmaceutical Sciences, 17th ed. (1990), Mack Publishing Co., Easton, Penn.; Avis, et al. (eds. 1993) Pharmaceutical Dosage Forms: Parenteral Medications, Dekker, New York; Lieberman, et al. (eds. 1990) Pharmaceutical Dosage Forms: Tablets, Dekker, New York; and Lieberman, et al. (eds. 1990) Pharmaceutical Dosage Forms: Disperse Systems, Dekker, New York. The therapy of this invention may be combined with or used in association with other agents, e.g., other modulators of cell activation, e.g., CD40, CD40 ligand, CD28, CTLA-4, B7, B70, SLAM, T cell receptor signaling entities, or their respective antagonists.

Both the naturally occurring and the recombinant forms of the proteins of this invention are particularly useful in kits and assay methods which are capable of screening compounds for binding activity to the proteins. Several methods of automating assays have been developed in recent years so as to permit screening of tens of thousands of compounds in a short period. See, e.g., Fodor, et al. (1991) Science 251:767-773, which describes means for testing of binding affinity by a plurality of defined polymers synthesized on a solid substrate. The development of suitable assays can be greatly facilitated by the availability of large amounts of purified, soluble proteins or nucleic acids as provided by this invention.

Other methods can be used to determine the critical residues in the substrate, ligand, or receptor binding interactions. Mutational analysis can be performed, e.g., see Somoza, et al. (1993) J. Exp. Med. 178:549-558, to determine specific residues critical in the interaction and/or signaling. This will allow study of both extracellular domains, involved in the soluble ligand interaction, or intracellular domain of a transmembrane form, which provides interactions important in intracellular signaling.

For example, antagonists can normally be found once the antigen has been structurally defined, e.g., by tertiary structure data. Testing of potential interacting analogs is now possible

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upon the development of highly automated assay methods using a purified protein. In particular, new agonists and antagonists will be discovered by using screening techniques described herein. Of particular importance are compounds found to have a combined
5 binding affinity for a spectrum of protein molecules, e.g., compounds which can serve as antagonists for species variants of the antigens.

One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with
10 recombinant DNA molecules expressing desired protein. Cells may be isolated which express a selected protein in isolation from other molecules. Such cells, either in viable or fixed form, can be used for standard binding partner binding assays. See also, Parce, et al. (1989) Science 246:243-247; and Owicki, et al.
15 (1990) Proc. Nat'l Acad. Sci. USA 87:4007-4011, which describe sensitive methods to detect cellular responses.

Another technique for drug screening involves an approach which provides high throughput screening for compounds having suitable binding affinity to a desired target protein, and is
20 described in detail in Geysen, European Patent Application 84/03564, published on September 13, 1984. First, large numbers of different small peptide test compounds are synthesized on a solid substrate, e.g., plastic pins or some other appropriate surface, see Fodor, et al. (1991). Then the pins are reacted with
25 solubilized, unpurified or solubilized, purified target protein, and washed. The next step involves detecting bound protein.

Rational drug design may also be based upon structural studies of the molecular shapes of the protein and other effectors or analogs. Effectors may be other proteins which mediate other
30 functions in response to binding, or other proteins which normally interact. One means for determining which sites interact with specific other proteins is a physical structure determination, e.g., x-ray crystallography or 2 dimensional NMR techniques. These will provide guidance as to which amino acid residues form
35 molecular contact regions. For a detailed description of protein structural determination, see, e.g., Blundell and Johnson (1976) Protein Crystallography, Academic Press, New York.

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IX. Kits

This invention also contemplates use of the proteins, fragments thereof, peptides, and their fusion products in a variety of diagnostic kits and methods for detecting, e.g., the presence of protein or binding partner. Typically the kit will have a compartment containing either a described polypeptide or gene segment or a reagent which recognizes one or the other, e.g., fragments or antibodies. Alternatively, kits may be nucleic acid based.

A kit for determining the binding affinity of a test compound to, e.g., an HDTEA84, would typically comprise a test compound; a labeled compound, for example a binding partner or antibody having known binding affinity for HDTEA84; a source of HDTEA84 (naturally occurring or recombinant); and a means for separating bound from free labeled compound, such as a solid phase for immobilizing the molecule. Once compounds are screened, those having suitable binding affinity to the antigen can be evaluated in suitable biological assays, as are well known in the art, to determine whether they act as agonists or antagonists to the HDTEA84 signaling pathway. The availability of recombinant HDTEA84 polypeptides also provide well defined standards for calibrating such assays.

A preferred kit for determining the concentration of, e.g., an HDTEA84 in a sample would typically comprise a labeled compound, e.g., binding partner or antibody, having known binding affinity for the antigen, a source of antigen (naturally occurring or recombinant) and a means for separating the bound from free labeled compound, e.g., a solid phase for immobilizing the HDTEA84. Compartments containing reagents, and instructions, will normally be provided.

Antibodies, including antigen binding fragments, specific for, e.g., the HDTEA84 or fragments, are useful in diagnostic applications to detect the presence of elevated levels of HDTEA84 and/or its fragments. Such diagnostic assays can employ lysates, live cells, fixed cells, immunofluorescence, cell cultures, body fluids, and further can involve the detection of antigens related

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to the antigen in serum, or the like. Diagnostic assays may be homogeneous (without a separation step between free reagent and antigen-binding partner complex) or heterogeneous (with a separation step). Various commercial assays exist, such as
5 radioimmunoassay (RIA), enzyme-linked immunosorbent assay (ELISA), enzyme immunoassay (EIA), enzyme-multiplied immunoassay technique (EMIT), substrate-labeled fluorescent immunoassay (SLFIA), and the like. See, e.g., Van Vunakis, et al. (1980) Meth Enzymol. 70:1-525; Harlow and Lane (1980) Antibodies: A Laboratory Manual, CSH
10 Press, NY; and Coligan, et al. (eds. 1993) Current Protocols in Immunology, Greene and Wiley, NY.

Anti-idiotypic antibodies may have similar use to diagnose presence of antibodies against a described protein, as such may be diagnostic of various abnormal states. Overproduction of
15 prostaglandin transporter may reflect various medical conditions, which may be diagnostic of abnormal physiological states, particularly in proliferative cell conditions such as cancer or abnormal differentiation. For example, leukemias and lymphomas may exhibit altered transporter expression, which may reflect
20 their altered physiology and may provide means to selectively target. Alternatively, overproduction of HDTEA84, HSLJD37R, RANKL, HCC5, MD-1, or MD-2 may result in production of various immunological reactions which may be diagnostic of abnormal physiological states, particularly in proliferative cell
25 conditions such as cancer or abnormal activation or differentiation. Expression levels of DC-PGT, Dubs, or cyclin E2 may likewise be diagnostic of specific therapeutic conditions, advantageous or disadvantageous.

Frequently, the reagents for diagnostic assays are supplied
30 in kits, so as to optimize the sensitivity of the assay. For the subject invention, depending upon the nature of the assay, the protocol, and the label, either labeled or unlabeled antibody or binding partner, or labeled HDTEA84 is provided. This is usually in conjunction with other additives, such as buffers, stabilizers,
35 materials necessary for signal production such as substrates for enzymes, and the like. Preferably, the kit will also contain instructions for proper use and disposal of the contents after

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use. Typically the kit has compartments for each useful reagent. Desirably, the reagents are provided as a dry lyophilized powder, where the reagents may be reconstituted in an aqueous medium providing appropriate concentrations of reagents for performing the assay.

Many of the aforementioned constituents of the drug screening and the diagnostic assays may be used without modification or may be modified in a variety of ways. For example, labeling may be achieved by covalently or non-covalently joining a moiety which directly or indirectly provides a detectable signal. In these assays, the binding partner, test compound, HDTEA84, or antibodies thereto can be labeled either directly or indirectly.

Possibilities for direct labeling include label groups:

radiolabels such as ^{125}I , enzymes (U.S. Pat. No. 3,645,090) such as peroxidase and alkaline phosphatase, and fluorescent labels (U.S. Pat. No. 3,940,475) capable of monitoring the change in fluorescence intensity, wavelength shift, or fluorescence polarization. Possibilities for indirect labeling include biotinylation of one constituent followed by binding to avidin coupled to one of the above label groups.

There are also numerous methods of separating the bound from the free polypeptide, or alternatively the bound from the free test compound. The polypeptide can be immobilized on various matrixes followed by washing. Suitable matrices include plastic such as an ELISA plate, filters, and beads. See, e.g., Coligan, et al. (eds. 1993) Current Protocols in Immunology, Vol. 1, Chapter 2, Greene and Wiley, NY. Other suitable separation techniques include, without limitation, the fluorescein antibody magnetizable particle method described in Rattle, et al. (1984) Clin. Chem. 30:1457-1461, and the double antibody magnetic particle separation as described in U.S. Pat. No. 4,659,678.

Methods for linking proteins or their fragments to the various labels have been extensively reported in the literature and do not require detailed discussion here. Many of the techniques involve the use of activated carboxyl groups either through the use of carbodiimide or active esters to form peptide bonds, the formation of thioethers by reaction of a mercapto group

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with an activated halogen such as chloroacetyl, or an activated olefin such as maleimide, for linkage, or the like. Fusion proteins will also find use in these applications.

Another diagnostic aspect of this invention involves use of
5 oligonucleotide or polynucleotide sequences taken from the
sequence of a described protein. These sequences can be used as
probes for detecting levels of the message in samples from
patients suspected of having an abnormal condition, e.g., cancer
or developmental problem. Since the antigen is a marker for
10 activation, it may be useful to determine the numbers of activated
T cells to determine, e.g., when additional suppression may be
called for. The preparation of both RNA and DNA nucleotide
sequences, the labeling of the sequences, and the preferred size
of the sequences has received ample description and discussion in
15 the literature. See, e.g., Langer-Safer, et al. (1982) Proc.
Nat'l. Acad. Sci. 79:4381-4385; Caskey (1987) Science 236:962-967;
and Wilchek, et al. (1988) Anal. Biochem. 171:1-32.

Alternatively, antibodies may be employed which can recognize
specific duplexes, including DNA duplexes, RNA duplexes, DNA-RNA
20 hybrid duplexes, or DNA-protein duplexes. The antibodies in turn
may be labeled and the assay carried out where the duplex is bound
to a surface, so that upon the formation of duplex on the surface,
the presence of antibody bound to the duplex can be detected. The
use of probes to the novel anti-sense RNA may be carried out in
25 any conventional techniques such as nucleic acid hybridization,
plus and minus screening, recombinational probing, hybrid released
translation (HRT), and hybrid arrested translation (HART). This
also includes amplification techniques such as polymerase chain
reaction (PCR).

30 Diagnostic kits which also test for the qualitative or
quantitative presence of other markers are also contemplated.
Diagnosis or prognosis may depend on the combination of multiple
indications used as markers. Thus, kits may test for combinations
of markers. See, e.g., Viallet, et al. (1989) Progress in Growth
35 Factor Res. 1:89-97. Other kits may be used to evaluate T cell
subsets.

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X. Methods for Isolating Substrates/Specific Partners

The DC-PGT should interact with its substrate target. The substrate will be similar to the organic molecules which are subject to transport. The Dubs and cyclin E2 will also be
5 screened for substrate identification.

The HDTEA84, HSLJD37R, and RANKL protein should interact with a TNF ligand, based, e.g., upon its similarity in structure and function to other cell surface antigens exhibiting similar structure and cell type specificity of expression. The MD-1 and
10 MD-2 antigens are related to known proteins, which interact with B cell antigens. Methods to isolate a ligand are made available by the ability to make purified protein for screening programs. Similar techniques will be applicable to the HCC5 chemokine, and the MD-1 and MD-2 surface receptors.

Sequences provided herein will allow for screening or
15 isolation of specific ligands. Many methods exist for expression cloning, panning, affinity isolation, or other means to identify a ligand. A two-hybrid selection system may also be applied making appropriate constructs with the available sequences, as
20 appropriate. See, e.g., Fields and Song (1989) Nature 340:245-246.

The broad scope of this invention is best understood with reference to the following examples, which are not intended to limit the invention to specific embodiments.

EXAMPLES

General Methods

Some of the standard methods are described or referenced, e.g., in Maniatis, et al. (1982) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor Press; Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual (2d ed.), vols. 1-3, CSH Press, NY; Ausubel, et al., Biology, Greene Publishing Associates, Brooklyn, NY; or Ausubel, et al. (1987 and Supplements) Current Protocols in Molecular Biology, Greene and Wiley, New York; Innis, et al. (eds. 1990) PCR Protocols: A Guide to Methods and Applications, Academic Press, N.Y. Methods for protein purification include such methods as ammonium sulfate precipitation, column chromatography, electrophoresis, centrifugation, crystallization, and others. See, e.g., Ausubel, et al. (1987 and periodic supplements); Deutscher (1990) "Guide to Protein Purification" in Methods in Enzymol. vol. 182, and other volumes in this series; and manufacturer's literature on use of protein purification products, e.g., Pharmacia, Piscataway, N.J., or Bio-Rad, Richmond, CA. Combination with recombinant techniques allow fusion to appropriate segments, e.g., to a FLAG sequence or an equivalent which can be fused via a protease-removable sequence. See, e.g., Hochuli (1990) "Purification of Recombinant Proteins with Metal Chelate Absorbent" in Setlow (ed.) Genetic Engineering, Principle and Methods 12:87-98, Plenum Press, N.Y.; and Crowe, et al. (1992) OIAexpress: The High Level Expression & Protein Purification System QIAGEN, Inc., Chatsworth, CA. Cell culture techniques are described in Doyle, et al. (eds. 1994) Cell and Tissue Culture: Laboratory Procedures, John Wiley and Sons, NY.

Standard immunological techniques are described, e.g., in Hertenzenberg, et al. (eds. 1996) Weir's Handbook of Experimental Immunology vols. 1-4, Blackwell Science; Coligan (1991) Current Protocols in Immunology Wiley/Greene, NY; and Methods in Enzymology volumes. 70, 73, 74, 84, 92, 93, 108, 116, 121, 132, 150, 162, and 163.

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FACS analyses are described in Melamed, et al. (1990) Flow Cytometry and Sorting Wiley-Liss, Inc., New York, NY; Shapiro (1988) Practical Flow Cytometry Liss, New York, NY; and Robinson, et al. (1993) Handbook of Flow Cytometry Methods Wiley-Liss, New York, NY. Fluorescent labeling of appropriate reagents was performed by standard methods.

The FASTA (Pearson and Lipman, 1988) and BLAST (Altschul, et al. (1990) J. Mol. Biol. 215:403-410) programs were used to comb nonredundant protein and nucleotide databases (Benson, et al. (1994) Nucl. Acids Res. 22:3441-3444; Bairoch and Boeckmann (1994) Nucl. Acids Res. 22:3578-3580) with the resultant cDNA and encoded protein sequences. The sensitive search strategies of Altschul, et al. (1994) Nature Genet. 6:119-129; and Koonin, et al. (1994) EMBO J. 13:493-503; served as examples of how to locate distant structural homologues of protein chains. Multiple alignments of collected homologues were carried out with ClustalW (Thompson, et al. (1994) Comp. Applic. Biosci. 10:19-29) and MACAW (Schuler, et al. (1991) Proteins 9:180-190).

The membrane topologies of proteins, e.g., DC-PGT, and a cohort of putative homologues were analyzed by a variety of methods that sought to determine the consensus number of domains, e.g., hydrophobic membrane-spanning helices and the likely cytoplasmic or extracellular exposure of the hydrophilic connecting loops. For single sequence analysis, the ALOM and MTOP (Klein, et al. (1985) Biochim. Biophys. Acta 815:468-476; and Hartmann, et al. (1989) Proc. Natl. Acad. Sci. USA 86:5786-5790) programs were accessed from the PSORT World-Wide Web site (Nakai and Kanehisa (1991) Proteins 11:95-110; and Nakai and Kanehisa (1992) Genomics 14:897-911); in turn, the TopPredII program (Claros and von Heijne (1994) Comp. Applic. Biosci. 10:685-686; MacIntosh PPC version) was used to parse chains into probable hydrophobic transmembrane and loop regions of DC-PGT, and further predict the localization of these latter regions by prevalence of charged residue types (von Heijne (1992) J. Mol. Biol. 225:487-494; and Sippos and von Heijne (1993) Eur. J. Biochem. 213:1333-

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1340). MEMSAT (Jones, et al. (1994) Biochem. 33:3038-3049; MS-DOS PC version) was likewise used to fit individual sequences into statistically-based topology models that render judgment on membrane spanning and loop chain segments. Two Web-accessible programs that are able to make use of evolutionary data by analyzing multiply aligned sequences are PHD (Rost, et al. (1994) Comp. Applic. Biosci. 10:53-60; and Rost, et al. (1995) Protein Sci. 4:521-533) and TMAP (Persson and Argos (1994) J. Mol. Biol. 237:182-192); the former utilizes a neural network system to accurately predict the shared location of helical transmembrane segments in a protein family. Similar analysis of other proteins can be performed.

I. Generation of Dendritic Cells

Human CD34+ cells are obtained as follows. See, e.g., Caux, et al. (1995) pages 1-5 in Banchereau and Schmitt Dendritic Cells in Fundamental and Clinical Immunology Plenum Press, NY. Peripheral or cord blood cells, sometimes CD34+ selected, are cultured in the presence of Stem Cell Factor (SCF), GM-CSF, and TNF- α in endotoxin free RPMI 1640 medium (GIBCO, Grand Island, NY) supplemented with 10% (v/v) heat-inactivated fetal bovine serum (FBS; Flow Laboratories, Irvine, CA), 10 mM HEPES, 2 mM L-glutamine, 5 X 10⁻⁵ M 2-mercaptoethanol, penicillin (100 μ g/ml). This is referred to as complete medium.

CD34+ cells are seeded for expansion in 25 to 75 cm² flasks (Corning, NY) at 2 x 10⁴ cells/ml. Optimal conditions are maintained by splitting these cultures at day 5 and 10 with medium containing fresh GM-CSF and TNF- α (cell concentration: 1-3 x 10⁵ cells/ml). In certain cases, cells are FACS sorted for CD1a expression at about day 6.

In certain situations, cells are routinely collected after 12 days of culture, eventually adherent cells are recovered using a 5 mM EDTA solution. In other situations, the CD1a+ cells are activated by resuspension in complete medium at 5 x 10⁶ cells/ml and activated for the appropriate time (e.g., 1 or 6 h) with 1

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µg/ml phorbol 12-myristate 13-acetate (PMA, Sigma) and 100 ng/ml ionomycin (Calbiochem, La Jolla, CA). These cells are expanded for another 6 days, and RNA isolated for cDNA library preparation.

Other specific cell types may be similarly isolated.

5

II. RNA Isolation and Library Construction

Total RNA is isolated using, e.g., the guanidine thiocyanate/CsCl gradient procedure as described by Chirgwin, et al. (1978) Biochem. 18:5294-5299.

10

Alternatively, poly(A)+ RNA is isolated using the OLIGOTEX mRNA isolation kit (QIAGEN). Double stranded cDNA are generated using, e.g., the SUPERScript plasmid system (Gibco BRL, Gaithersburg, MD) for cDNA synthesis and plasmid cloning. The resulting double stranded cDNA is unidirectionally cloned, e.g., into pSport1 and transfected by electroporation into ELECTROMAX DH10BTM Cells (Gibco BRL, Gaithersburg, MD).

15

III. Sequencing

20

DNA isolated from randomly picked clones, or after subtractive hybridization using inactivated cells, are subjected to nucleotide sequence analysis using standard techniques.

25

Alternatively, selected isolated clones can be selected. A Taq DiDeoxy Terminator cycle sequencing kit (Applied Biosystems, Foster City, CA) can be used. The labeled DNA fragments are separated using a DNA sequencing gel of an appropriate automated sequencer. Alternatively, the isolated clone is sequenced as described, e.g., in Maniatis, et al. (Current ed.) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor Press; Sambrook, et al. (Current ed.) Molecular

30

Cloning: A Laboratory Manual, (2d ed.), vols. 1-3, CSH Press, NY; Ausubel, et al., Biology, Greene Publishing Associates, Brooklyn, NY; or Ausubel, et al. (Current ed., and Supplements) Current Protocols in Molecular Biology, Greene/Wiley, New York. Chemical sequencing methods are also available, e.g., using Maxim and Gilbert sequencing techniques.

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IV. Recombinant gene constructs

Poly(A)⁺ RNA is isolated from appropriate cell populations, e.g., using the FastTrack mRNA kit (Invitrogen, San Diego, CA). Samples are electrophoresed, e.g., in a 1% agarose gel containing formaldehyde and transferred to a GeneScreen membrane (NEN Research Products, Boston, MA). Hybridization is performed, e.g., at 65° C in 0.5 M NaHPO₄ pH 7.2, 7% SDS, 1 mM EDTA, and 1% BSA (fraction V) with ³²P-dCTP labeled DC gene cDNA at 10⁷ cpm/ml. After hybridization, filters are washed three times at 50° C in 0.2X SSC, 0.1% SDS, e.g., for 30 min, and exposed to film for 24 h. A positive signal will typically be 2X over background, preferably 5-25X.

The recombinant gene construct may be used to generate a probe for detecting the message. The insert may be excised and used in the detection methods described above. Various standard methods for cross species hybridization and washes are well known in the art. See, e.g., Sambrook, et al. and Ausubel.

V: Gene Cloning

The HDTEA84 was assembled by careful analysis of ESTs found in various databases. These ESTs were from cDNA libraries derived from Hodgkin's lymphoma, endothelial cells, keratinocytes, prostate, and cerebellum. PCR primers are designed and synthesized and a PCR product is obtained from any of these libraries. This product is used as a hybridization clone to screen these libraries for a full length clone, which may include a transmembrane segment.

Likewise, the HSLJD37R was identified from sequences derived from cDNA libraries from: smooth muscle, pancreas tumor, adipocytes, HUVEC cells, adult pulmonary, endothelial cells, prostate cell line PC3, microvascular endothelial cells, fetal heart, and dendritic cells. A GenBank report by Pan, et al. has been submitted. See GenBank Accession 3549263. Other sequences were detected in libraries from: multiple sclerosis lesions, breast, kidney, and germinal center B cells. RT-PCT showed signal in B cells, PBL, granulocytes, T cells, monocytes, dendritic cell subpopulations including PMA/ionomycin treated, U937 cells, JY

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cells, MRC5 cells, CHA, Jurkat, and YC1 cells. This suggests that the transcript is widely expressed.

RANKL was also identified in cDNA libraries from specific tissues, as described. Likewise, the HCC5 chemokine sequence was identified. The Dub11 and Dub12 genes were identified, in part, from their similarity to known Dub1 and Dub2 genes. The MD-1 and MD-2 were identified, in part, from their similarity to the ligand for the RP105 gene. The cyclin E2 was identified based upon its similarity to cyclin E.

VI. Expression Profile

To examine DC-PGT mRNA expression standard Northern Blot Analysis using a RT-PCR fragment of DC-PGT were carried out against human tissue, e.g., Northern blots containing approximately 10 to 20 µg of total RNA are run in formaldehyde gels and transferred to Nytran membranes (Schleicher & Schuell, Keene, NH) by standard methods, and blots were hybridized with a labeled PCR fragment of DC-PGT and washed at 65° C. cDNA can be isolated from cells, embryonic tissues, and adult organs using RNazol solution (Tel-test, Inc., Friendswood, TX) according to manufacturer's instructions. Large amounts of plasmid DNA containing differential display PCR products are prepared using the QIAGEN Plasmid Maxi Kit (QIAGEN) following the manufacturer's instructions. Plasmid DNA is cut with EcoRI (Boehringer Mannheim) or BstXI (NE Biolabs, Mass.), gel extracted with the QIAEX gel extraction kit (QIAGEN) and random primed with [³²P]dCTP (Amersham) using the Prime-It II kit (Stratagene, La Jolla, CA), all in accordance with manufacturer's instructions. Various primers may be used to quantitate expression of message. Means to block DNA hybridization signal, or RNA isolation, will be applicable to quantitate roughly the amount of expression of appropriate RNAs.

The results revealed mRNA of one band at approximately 9.0 kB, another band at approximately 3.0 kB, and a 4.4 kB size which is consistent with the size predicted for the SEQ ID NO: 1 nucleic acid. The smaller mRNA product band could be an alternatively spliced form of SEQ ID NO: 1. DC-PGT is highly expressed in both

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activated and non-activated dendritic cells (DC), activated monocytes, activated granulocytes and adult lung. No expression was found in T or PBL cells (either activated or non-activated). Minor expression was detected in B cell (both activated and non-activated) and limited expression was detected in the brain. The results of the northern analysis suggests an expression in macrophages, rather than monocytes (Kuppfer cells in the liver, microglial cells in the brain, alveolar macrophages in the lung) particularly as there is no expression in PBL. Southern expression analysis carried out using common techniques confirmed the expression pattern revealed in the Northern analysis.

For example, the DC-PGT tissue distribution seems to have highest mRNA levels in kidney, placenta, liver, bone marrow, thymus, spleen, lung, and some in testis. This distribution corresponds to organs with especially important ion exchange features, e.g., Na, K, or Ca, or in hematopoietic organs. Generally, the expression is higher in fibroblast and hematopoietic cells compared to neuronal cells.

A probe specific for cDNA encoding the HDTEA84, HSLJD37R, or RANKL is used to determine tissue distribution of message encoding the antigen. Standard hybridization probes may be used to do a Northern analysis of RNA from appropriate sources, either cells, e.g., stimulated, or in various physiological states, in various tissues, e.g., spleen, liver, thymus, lung, etc., or in various species. Southern analysis of cDNA libraries may also provide valuable distribution information. Standard tissue blots or species blots are commercially available. Similar techniques will be useful for evaluating diagnostic or medical conditions which may correlate with expression in various cell types.

PCR analysis using appropriate primers may also be used. Antibody analysis, including immunohistochemistry or FACS, may be used to determine cellular or tissue distribution.

Southern blot analysis of primate cDNA libraries is performed on, e.g.,: U937 premonocytic line, resting (M100); elutriated monocytes, activated with LPS, IFN γ , anti-IL-10 for 4, 16 h pooled (M106); elutriated monocytes, activated with LPS, IFN γ , IL-10 for 4, 16 h pooled (M107); elutriated monocytes, activated LPS for 1 h

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(M108); elutriated monocytes, activated LPS for 6 h (M109); dendritic cells (DC) 30% CD1a+, from CD34+ GM-CSF, TNF α 12 days, resting; DC 70% CD1a+, from CD34+ GM-CSF, TNF α 12 days, resting (D101); DC 70% CD1a+, from CD34+ GM-CSF, TNF α 12 days, activated with PMA and ionomycin for 1 hr (D102); DC 70% CD1a+, from CD34+ GM-CSF, TNF α 12 days, activated with PMA and ionomycin for 6 hr (D103); DC 95% CD1a+, from CD34+ GM-CSF, TNF α 12 days activated with PMA and ionomycin for 1 or 6 hr, pooled; DC from monocytes GM-CSF, IL-4 5 days, resting (D107); DC from monocytes GM-CSF, IL-4 5 days, resting (D108); DC from monocytes GM-CSF, IL-4 5 days, activated TNF α , monocyte supe for 4, 16 h pooled (D110); EBV transfected B cell lines, resting; spleenocytes, resting; spleenocytes, activated with PMA and ionomycin; 20 NK clones resting, pooled; 20 NK clones activated with PMA and ionomycin, pooled; NKL clone, IL-2 treated; NK cytotoxic clone, resting; adipose tissue fetal 28 wk male (O108); brain fetal 28 wk male (O104); gallbladder fetal 28 wk male (O106); heart fetal 28 wk male (O103); small intestine fetal 28 wk male (O107); kidney fetal 28 wk male (O100); liver fetal 28 wk male (O102); lung fetal 28 wk male (O101); ovary fetal 25 wk female (O109); adult placenta 28 wk (O113); spleen fetal 28 wk male (O112); testes fetal 28 wk male (O111); uterus fetal 25 wk female (O110); TH0 clone Mot 72, resting (T102); T cell, TH0 clone Mot 72, activated with anti-CD28 and anti-CD3 for 3, 6, 12 h pooled (T103); T cell, TH0 clone Mot 72, anergic treated with specific peptide for 2, 7, 12 h pooled (T104); Th0 subtraction of resting from activated; T cell, TH1 clone HY06, resting (T107); T cell, TH1 clone HY06, activated with anti-CD28 and anti-CD3 for 3, 6, 12 h pooled (T108); T cell, TH1 clone HY06, anergic treated with specific peptide for 2, 6, 12 h pooled (T109); Th1 subtraction of resting from activated; T cell, TH2 clone HY935, resting (T110); T cell, TH2 clone HY935, activated with anti-CD28 and anti-CD3 for 2, 7, 12 h pooled (T111); and Th2 subtraction of resting from activated.

Samples for mouse mRNA distribution may include, e.g., :
resting mouse fibroblastic L cell line (C200); Braf:ER (Braf

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fusion to estrogen receptor) transfected cells, control (C201); T cells, TH1 polarized (Mel14 bright, CD4+ cells from spleen, polarized for 7 days with IFN- γ and anti IL-4; T200); T cells, TH2 polarized (Mel14 bright, CD4+ cells from spleen, polarized for 7 days with IL-4 and anti-IFN- γ ; T201); T cells, highly TH1 polarized (see Openshaw, et al. (1995) J. Exp. Med. 182:1357-1367; activated with anti-CD3 for 2, 6, 16 h pooled; T202); T cells, highly TH2 polarized (see Openshaw, et al. (1995) J. Exp. Med. 182:1357-1367; activated with anti-CD3 for 2, 6, 16 h pooled; T203); CD44- CD25+ pre T cells, sorted from thymus (T204); TH1 T cell clone D1.1, resting for 3 weeks after last stimulation with antigen (T205); TH1 T cell clone D1.1, 10 μ g/ml ConA stimulated 15 h (T206); TH2 T cell clone CDC35, resting for 3 weeks after last stimulation with antigen (T207); TH2 T cell clone CDC35, 10 μ g/ml ConA stimulated 15 h (T208); Mel 14+ naive T cells from spleen, resting (T209); Mel14+ T cells, polarized to Th1 with IFN- γ /IL-12/anti-IL-4 for 6, 12, 24 h pooled (T210); Mel 14+ T cells, polarized to Th2 with IL-4/anti-IFN- γ for 6, 13, 24 h pooled (T211); unstimulated mature B cell leukemia cell line A20 (B200); unstimulated B cell line CH12 (B201); unstimulated large B cells from spleen (B202); B cells from total spleen, LPS activated (B203); metrizamide enriched dendritic cells from spleen, resting (D200); dendritic cells from bone marrow, resting (D201); monocyte cell line RAW 264.7 activated with LPS 4 h (M200); bone-marrow macrophages derived with GM and M-CSF (M201); macrophage cell line J774, resting (M202); macrophage cell line J774 + LPS + anti-IL-10 at 0.5, 1, 3, 6, 12 h pooled (M203); macrophage cell line J774 + LPS + IL-10 at 0.5, 1, 3, 5, 12 h pooled (M204); aerosol challenged mouse lung tissue, Th2 primers, aerosol OVA challenge 7, 14, 23 h pooled (see Garlisi, et al. (1995) Clinical Immunology and Immunopathology 75:75-83; X206); Nippostrongylus-infected lung tissue (see Coffman, et al. (1989) Science 245:308-310; X200); total adult lung, normal (O200); total lung, rag-1 (see Schwarz, et al. (1993) Immunodeficiency 4:249-252; O205); IL-10 K.O. spleen (see Kuhn, et

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al. (1991) Cell 75:263-274; X201); total adult spleen, normal (O201); total spleen, rag-1 (O207); IL-10 K.O. Peyer's patches (O202); total Peyer's patches, normal (O210); IL-10 K.O. mesenteric lymph nodes (X203); total mesenteric lymph nodes, normal (O211); IL-10 K.O. colon (X203); total colon, normal (O212); NOD mouse pancreas (see Makino, et al. (1980) Jikken Dobutsu 29:1-13; X205); total thymus, rag-1 (O208); total kidney, rag-1 (O209); total heart, rag-1 (O202); total brain, rag-1 (O203); total testes, rag-1 (O204); total liver, rag-1 (O206); rat normal joint tissue (O300); and rat arthritic joint tissue (X300).
A. Direct protein detection by antibodies

Various cells, tissues, and developmental stages are stained with labeled antibodies. The detection may be immuno-histochemical for solid tissue, by FACS in disperse cells, and by other appropriate methods for other sample types. Antibodies specific for the various forms may be used to distinguish between membrane associated and soluble fragments. Various amplification means may be coupled to increase sensitivity.

B. Functional detection

Specific neutralizing antibodies should provide means to specifically block the biological activity of the prostaglandin transporter. Activities related to prostaglandin binding, or to prostaglandin transport may be measured by sensitive means based upon knowledge of the normal biological function of the various forms.

Further testing of populations of cells, e.g., hematopoietic progenitors, or of other cell or tissue types will be useful to further determine distribution and likely function. Other tissue types, at defined developmental stages, and pathology samples may be screened to determine whether pathological states or stages may be advantageously correlated with the biological activity of the transporter.

VII. Protein Expression

PCR is used to make a construct comprising the open reading frame, preferably in operable association with proper promoter, selection, and regulatory sequences. The resulting expression

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plasmid is transformed into an appropriate cell type, e.g., the Topp5, E. coli strain (Stratagene, La Jolla, CA). Ampicillin resistant (50 µg/ml) transformants are grown in Luria Broth (Gibco) at 37° C until the optical density at 550 nm is 0.7.

5 Recombinant protein is induced with 0.4 mM isopropyl-βD-thiogalacto-pyranoside (Sigma, St. Louis, MO) and incubation of the cells continued at 20° C for a further 18 hours. Cells from a 1 liter culture are harvested by centrifugation and resuspended, e.g., in 200 ml of ice cold 30% sucrose, 50 mM Tris
10 HCl pH 8.0, 1 mM ethylenediaminetetraacetic acid. After 10 min on ice, ice cold water is added to a total volume of 2 liters. After 20 min on ice, cells are removed by centrifugation and the supernatant is clarified by filtration via a 5 µM Millipak 60 (Millipore Corp., Bedford, MA).

15 The recombinant protein is purified via standard purification methods, e.g., various ion exchange chromatography methods. Immunoaffinity methods using antibodies described below can also be used. Affinity methods may be used where an epitope tag is engineered into an expression construct.

20 Similar methods are used to prepare expression constructs and cells in eukaryotic cells. Eukaryotic promoters and expression vectors may be produced, as described above.

Further study of the expression and control of prostaglandin transporter will be pursued. The controlling elements associated
25 with the antigens may exhibit differential developmental, tissue specific, or other expression patterns. Upstream or downstream genetic regions, e.g., control elements, are of interest.

Multiple transfected cell lines are screened for one which expresses the antigen, membrane bound, or soluble forms, at a high
30 level compared with other cells. Various cell lines are screened and selected for their favorable properties in handling. Natural protein can be isolated from natural sources, or by expression from a transformed cell using an appropriate expression vector. Purification of the expressed protein is achieved by standard
35 procedures, or may be combined with engineered means for effective purification at high efficiency from cell lysates or supernatants. FLAG or His₆ segments can be used for such purification features.

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VIII. Protein Purification

The prostaglandin transporter is isolated by a combination of affinity chromatography using the prostaglandin transporter specific binding compositions, e.g., antibody, as a specific binding reagent in combination with protein purification techniques allowing separation from other proteins and contaminants. Various detergent combinations may be tested to determine what combinations will retain biological activity while solubilizing contaminants. The purification may follow biological activity, e.g., prostaglandin binding or transport into membranes, or by ELISA or other structural binding reagents.

Similar methods are applied for purification of other polypeptides.

IX. Isolation of Homologous Genes

The described genes, e.g., cDNA, can be used as a hybridization probe to screen a library from a desired source, e.g., a primate cell cDNA library. Many different species can be screened both for stringency necessary for easy hybridization, and for presence using a probe. Appropriate hybridization conditions will be used to select for clones exhibiting specificity of cross hybridization.

cDNA libraries from the desired species are collected, from appropriate cell types. Screening by hybridization or PCR using degenerate probes based upon the peptide sequences will also allow isolation of appropriate clones. Alternatively, use of appropriate primers for PCR screening will yield enrichment of appropriate nucleic acid clones.

Similar methods are applicable to isolate either species, polymorphic, or allelic variants. Species variants are isolated using cross-species hybridization techniques based upon isolation of a full length isolate or fragment from one species as a probe.

Alternatively, antibodies raised against proteins will be used to screen for cells which express cross-reactive proteins from an appropriate, e.g., cDNA library. The purified protein or defined peptides are useful for generating antibodies by standard

methods, as described above. Synthetic peptides or purified protein are presented to an immune system to generate monoclonal or polyclonal antibodies. See, e.g., Coligan (1991) Current Protocols in Immunology Wiley/Greene; and Harlow and Lane (1989) Antibodies: A Laboratory Manual Cold Spring Harbor Press. The resulting antibodies are used, e.g., for screening, panning, or sorting.

X. Antibody Preparation

Synthetic peptides or purified protein, natural or recombinant, are presented to an immune system to generate monoclonal or polyclonal antibodies. See, e.g., Coligan (1991) Current Protocols in Immunology Wiley/Greene; and Harlow and Lane (1989) Antibodies: A Laboratory Manual Cold Spring Harbor Press. Polyclonal serum, or hybridomas may be prepared. In appropriate situations, the binding reagent is either labeled as described above, e.g., fluorescence or otherwise, or immobilized to a substrate for panning methods.

XI. Chromosome Mapping

DNA isolation, restriction enzyme digestion, agarose gel electrophoresis, Southern blot transfer and hybridization are performed according to standard techniques. See Jenkins, et al. (1982) J. Virol. 43:26-36. Blots may be prepared with Hybond-N nylon membrane (Amersham). The probe is labeled with ^{32}P -dCTP; washing is done to a final stringency, e.g., of 0.1X SSC, 0.1% SDS, 65° C.

Alternatively, a BIOS Laboratories (New Haven, CT) mouse somatic cell hybrid panel may be combined with PCR methods. See Fan, et al. (1996) Immunogenetics 44:97-103.

Chromosome spreads are prepared. In situ hybridization is performed on chromosome preparations obtained from phytohemagglutinin-stimulated human lymphocytes cultured for 72 h. 5-bromodeoxyuridine is added for the final seven hours of culture (60 µg/ml of medium), to ensure a posthybridization chromosomal banding of good quality.

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A PCR fragment, amplified with the help of primers, is cloned into an appropriate vector. The vector is labeled by nick-translation with ^3H . The radiolabeled probe is hybridized to metaphase spreads at final concentration of 200 ng/ml of

5 hybridization solution as described in Mattei, et al. (1985) Hum. Genet. 69:327-331.

After coating with nuclear track emulsion (KODAK NTB2), slides are exposed. To avoid any slipping of silver grains during the banding procedure, chromosome spreads are first stained with
10 buffered Giemsa solution and metaphase photographed. R-banding is then performed by the fluorochrome-photolysis-Giemsa (FPG) method and metaphases rephotographed before analysis.

Using these techniques, the DC-PGT gene was mapped to marker SHGC-3911 on chromosome 11q13 with a resulting lod score of
15 1000.0. Other markers in the SHGC-3911 region at chromosome 11q13 include the FcεRI receptor which is alleged to be associated with allergic conditions. In comparison to the location of DC-PGT, the ubiquitously expressed human PGT homologue of Lu et al., (described above) is localized to chromosome 7.

20

XII. Biochemical Characterization

Constructs for the expression of, e.g., DC-PGT are made with a tag (FLAG) sequence (Hopp, et al. (1988) Biotechnology (NY) 6:1205-1210) introduced in the protein. The open reading frame of
25 the DC-PGT cDNA of SEQ ID NO: 1 is amplified by appropriate PCR primers using standard methods to introduce the FLAG peptide sequence (IBI, New Haven, CT) at the C-terminus of the protein. For example, a PFU enzyme (Stratagene) with 12 cycles PCR: 94° C 30 sec; 55° C 1 min; 72° C 4 min. PCR constructs are cloned into
30 a PME18X vector (DNAX) using XhoI and XbaI sites incorporated into the 5' and 3' primers, respectively.

COS-7 cells are maintained in DMEM, 10% FCS, 4 mM L-glutamine (JRH Biosciences, Lenexa, KS), 100 U/ml penicillin, and 100 µg/ml streptomycin. Plasmid DNA is transfected by electroporation
35 (BIORAD, Hercules, CA) (20 µg / 1×10^7 cells) and plated into tissue culture dishes. The medium is replaced after 24 hours and

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cell lysates and media are collected three days after transfection. Lysis buffer (25 mM Hepes pH 7.5, 2 mM EDTA, 1.0% NP-40, 150 mM NaCl, 0.01% Aprotinin (Sigma, St. Louis, MO), 0.01% Leupeptin (Sigma)) is added to the plates. Plates are kept on ice for 45 minutes. Lysates are centrifuged for 15 minutes to eliminate cell debris. Supernatants of centrifuged cell lysates and sterile-filtered media from cultured cells are incubated with anti-FLAG M2 Affinity Gel (IBI) at 4° C overnight and washed four times with PBS. Immunoprecipitates are eluted in a Econocolumn (BIORAD) with 2.5 M Glycine, pH 2.5. Eluates are neutralized with Hepes, pH 7.4 (JRH Biosciences) and concentrated by precipitation with 24% TCA and 2% deoxycholic sodium salt (Sigma). Pellets are eluted in 2 x Sample Buffer (NOVEX, San Diego, CA), electrophoresed on 4-20% tris-glycine gels (Novex) and transferred to PVDF membranes (Immobilon-P, Millipore Corporation, Bedford, MA). Membranes are exposed to 3% non-fat milk for 1 h at 37° C. Anti-FLAG M2 antibody is used as recommended (IBI). Anti-mouse Ig horseradish peroxidase conjugate (Amersham) is used at 1:2,000 dilution and the peroxidase detection is performed with ECL detection reagents (Amersham).

Other fusion proteins can be produced, e.g., a recombinant prostaglandin transporter construct is prepared, e.g., as a fusion product with a useful affinity reagent, e.g., FLAG peptide. This peptide segment may be useful for purifying the expression product of the construct. See, e.g., Crowe, et al. (1992) OIAexpress: The High Level Expression & Protein Purification System QUIAGEN, Inc. Chatsworth, CA; and Hopp, et al. (1988) Bio/Technology 6:1204-1210. Membranes comprising the transporter are assayed to determine the natural prostaglandin substrate. Most likely the prostaglandin will be a uracil related prostaglandin, but may also include, at various levels of efficiency of binding or transport, pyrimidine or purine analogs. See, e.g., Goodman and Gilman (Current ed.), The Pharmacological Basis of Therapeutics; Lukovics and Zablocka Nucleoside Synthesis: Organosilicon Methods Ellis Horwood, N.Y.; Townsend, Chemistry of Nucleosides and Nucleotides, vols. 1-3, Plenum Press, N.Y.; Munch-Pertson (1983) Metabolism of Nucleotides, Nucleosides, and Prostaglandins in Microorganisms

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Academic Press, NY; Gehrke (1990) Chromatography & Modification of Nucleosides vols. A, B, and C, Elsevier; Bloch (1975) Chemistry, Biology, & Clinical Uses of Nucleoside Analogs Annals NY Acad. Sci.; and Ulbricht (1964) Purines, Pyrimidines, & Nucleotides
5 Franklin Co.

XIII. Expression Cloning; Partner Screening

A. Antibodies and flow-cytometric sorting

Expression cloning of cells transformed with an appropriate
10 cDNA library may be sorted by FACS using antibody reagents described above. The sorted cells are isolated and expanded, and subjected to multiple selection cycles, leading to a high proportion of cells expressing the desired DNA.

B. Antibodies and staining

15 The antibodies to, e.g., DC-PGT, are used for screening of a library made from a cell line which expresses the polypeptide. Standard staining techniques are used to detect or sort intracellular or surface expressed ligand, or surface expressing transformed cells are screened by panning. Screening of
20 intracellular expression is performed by various staining or immunofluorescence procedures. See also McMahan, et al. (1991) EMBO J. 10:2821-2832.

For example, on day 0, precoat 2-chamber permanox slides with
1 ml per chamber of fibronectin, 10 ng/ml in PBS, for 30 min at
25 room temperature. Rinse once with PBS. Then plate COS cells at $2-3 \times 10^5$ cells per chamber in 1.5 ml of growth media. Incubate overnight at 37° C.

On day 1 for each sample, prepare 0.5 ml of a solution of 66
µg/ml DEAE-dextran, 66 µM chloroquine, and 4 µg DNA in serum free
30 DME. For each set, a positive control is prepared, e.g., of huIL-10-FLAG cDNA at 1 and 1/200 dilution, and a negative mock. Rinse cells with serum free DME. Add the DNA solution and incubate 5 hr at 37° C. Remove the medium and add 0.5 ml 10% DMSO in DME for 2.5 min. Remove and wash once with DME. Add 1.5 ml growth medium
35 and incubate overnight.

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On day 2, change the medium. On days 3 or 4, the cells are fixed and stained. Rinse the cells twice with Hank's Buffered Saline Solution (HBSS) and fix in 4% paraformaldehyde (PFA)/glucose for 5 min. Wash 3X with HBSS. The slides may be stored at -80° C after all liquid is removed. For each chamber, 0.5 ml incubations are performed as follows. Add HBSS/saponin (0.1%) with 32 µl/ml of 1M NaN₃ for 20 min. Cells are then washed with HBSS/saponin 1X. Soluble antibody is added to cells and incubate for 30 min. Wash cells twice with HBSS/saponin. Add second antibody, e.g., Vector anti-mouse antibody, at 1/200 dilution, and incubate for 30 min. Prepare ELISA solution, e.g., Vector Elite ABC horseradish peroxidase solution, and preincubate for 30 min. Use, e.g., 1 drop of solution A (avidin) and 1 drop solution B (biotin) per 2.5 ml HBSS/saponin. Wash cells twice with HBSS/saponin. Add ABC HRP solution and incubate for 30 min. Wash cells twice with HBSS, second wash for 2 min, which closes cells. Then add Vector diaminobenzoic acid (DAB) for 5 to 10 min. Use 2 drops of buffer plus 4 drops DAB plus 2 drops of H₂O₂ per 5 ml of glass distilled water. Carefully remove chamber and rinse slide in water. Air dry for a few minutes, then add 1 drop of Crystal Mount and a cover slip. Bake for 5 min at 85-90° C.

Alternatively, the antibodies to a selected protein are used to affinity purify or sort out cells expressing the antigen. See, e.g., Sambrook et al. or Ausubel et al, which are incorporated herein by reference. The antigen is typically expressed on the cell surface.

Hybridization approaches may also be utilized to find closely related variants of the antigen based upon nucleic acid hybridization.

XIV. Screening for DC-PGT Substrate Specificity

The types of organic anions transported by DC-PGT of the present invention can be directly tested using standard methods. For example, DC-PGT cDNAs can be expressed in HeLa cell monolayers or in Xenopus oocytes to determine the ability of DC-PGT to uptake various tracer labeled substrates e.g., prostaglandins such as PGE1, PGE2, PGE2a, PGD2, thromboxanes such as Tx_{B2} or non-

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prostaglandin anionic substrates such as glutathione, p-amino hippurate, taurochoalate, urate, unconjugated and conjugated bilirubin, and estradiol glucouronide. For example, for oocyte expression, water or complementary RNA (cRNA) that has been

5 transcribed in vitro from DC-PGT cDNA and capped is injected into *Xenopus* oocytes at approximately 50 ng of cRNA per oocyte. Uptake studies are performed 2 to 3 days after injection by washing of oocytes three times in Waymouth's solution, incubating for various periods at 27°C with radioactive substrates (approx. 0.25 μ Ci/ml;

10 total concentration, approx. 1 nM), washing three times with ice-cold Waymouth's solution, and lysing in 0.5 ml of 10% SDS. Oocyte-associated radioactivity is determined by liquid scintillation spectroscopy. For HeLa cell expression, cells are grown to approx. 80% confluence on 35 mm dishes then infected with

15 recombinant vaccinia virus vTF7-3 of 10 plaque forming units per cell according to a method of Fuesst, et al. (1986) Proc. Nat'l Acad. Sci. USA 83:8122-8126. Thirty minutes after infection cells are transfected with DC-PGT cDNA (10 μ g/ml) plus lipofectin (20 μ g/ml) according to a method of Blakely, et al. (1991) Anal.

20 Biochem. 194:302-310. After 3 hours of incubation, vaccinia virus and the DNA-lipofectin complex are removed, and the cells are maintained overnight in Dulbecco's modified Eagle's medium supplemented with 5% fetal bovine serum. Uptake studies are performed 19 hours after transfection. Monolayers are washed

25 three times with culture medium without serum and incubated for various times at 27° C with radioactive substrate (0.5 μ Ci/ml per dish; total concentration, approx. 0.2 nM). Uptake is stopped by washing cells once with ice-cold Waymouth's solution containing 5% bovine serum albumin and then four times with Waymouth's solution

30 alone. Cells are scrapped and the associated radioactivity is measured by liquid scintillation spectroscopy.

XV. Measuring DC-PGT Substrate Uptake Kinetics

Competitive tracer uptake kinetics using DC-PGT comparing

35 various prostaglandins or thromboxanes (e.g., PGE1, PGE2, PGE2a, PGD2 or TxB2) are determined using standard competitive transport

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assays. For example for determining time dependent uptake of tracer labeled prostaglandin uptakes into HeLa cells expressing DC-PGT clones the following $^3\text{[H]}$ -PGs final concentrations are used (New England Nuclear, Boston, MA): PGE₂: 0.7 nM (176 cpm/fmol);
5 PGE₁: 0.6 nM (62 cpm/fmol); PGD₂: 0.9 nM (126 cpm/fmol); PGF₂ α : 0.6 nM (185 cpm/fmol); TXB₂: 1.0 nM (114 cpm/fmol); PGI₂ analog $^3\text{[H]}$ -iloprost (Amersham Corp., Arlington Heights, IL) at 7.9 nM (14 cpm/fmol).

10 XVI. Determining DC-PGT uptake inhibition

Compositions inhibiting DC-PGT uptake can also be measured. For example to measure the inhibition of tracer PGE₂, uptakes at 10 min intervals (0.2 nM $^3\text{[H]}$ -PGE₂) with or without various concentrations of unlabeled prostanoids PGE₂, PGE₁, PGD₂, PGF₂ α ,
15 TXB₂, PGI₂, (100-500 nM; Cayman Chemical, Ann Arbor MI) or inhibitors such as furosemide, probenecid, and indomethacin (10-100 μM , Sigma Chemical Co., St. Louis, MO) are determined in duplicate on a given transfection for one or two separate transfections. Since the substrate concentrations are at least
20 500 times less than the concentration of unlabeled prostanoids an apparent affinity constant, $K_{1/2}$ is determined from the equation: $K_{1/2} = [v_i / (v - v_i)] [i]$ where v = uptake without inhibitor, v_i = uptake with inhibitor, and i = inhibitor concentration as described by Neame and Richards (1972) in Elementary Kinetics of
25 Membrane Carrier Transport, John Wiley & Sons, New York.

XVII. Screening for Agonists or Antagonists

Using a HeLa or Xenopus system, described above, or a comparable system, one of ordinary skill in the art can use the
30 DC-PGT of the invention to screen for inhibitors or agonists of DC-PGT mediated tracer transport. The efficacy of potential antagonists can be compared with known PG transport inhibitors such as furosemide, probenecid, or indomethacin. Potential agonist or antagonist compositions are incubated, using a system
35 as described above, for a time sufficient to allow binding of the

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test composition and the DC-PGT transporter. Enhancement or decrement in measures of tracer uptake can be correlated to the specific composition being tested. Accordingly, one can identify compounds or compositions that modulate organic anion transport via the DC-PGT transporter of the invention by assessing the uptake of various anions such as prostaglandins or thromboxanes in the presence and absence of the compound or compositions being tested. Similar methods may be used to screen for substrates for the enzymes, e.g., Dubs and cyclin E2.

XVIII. Isolation of Ligand for Receptor

A construct for expression of the product can be used as a specific binding reagent to identify its binding partner, e.g., ligand, by taking advantage of its specificity of binding, much like an antibody would be used. A receptor reagent is either labeled as described above, e.g., fluorescence or otherwise, or immobilized to a substrate for panning methods. See also Anderson, et al. (1997) Nature 390:175-179, which is incorporated herein by reference.

The binding composition is used to screen an expression library made from a cell line which expresses a binding partner, e.g., TNF family ligand. Standard staining techniques are used to detect or sort intracellular or surface expressed receptor, or surface expressing transformed cells are screened by panning. Screening of intracellular expression is performed by various staining or immunofluorescence procedures. See also McMahan, et al. (1991) EMBO J. 10:2821-2832.

Alternatively, receptor reagents are used to affinity purify or sort out cells expressing a receptor. See, e.g., Sambrook, et al. or Ausubel, et al.

Another strategy is to screen for a membrane bound ligand by panning. The cDNA containing ligand cDNA is constructed as described above. The ligand can be immobilized and used to immobilize expressing cells. Immobilization may be achieved by use of appropriate antibodies which recognize, e.g., a FLAG sequence or a receptor fusion construct, or by use of antibodies raised against the first antibodies. Recursive cycles of

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selection and amplification lead to enrichment of appropriate clones and eventual isolation of ligand expressing clones.

Phage expression libraries can be screened by receptor. Appropriate label techniques, e.g., anti-FLAG antibodies, will
5 allow specific labeling of appropriate clones.

IX. Chemotaxis Assays

Chemokine proteins are produced, e.g., in COS cells transfected with a plasmid carrying the chemokine cDNA by
10 electroporation. See, Hara, et al. (1992) EMBO J. 10:1875-1884. Physical analytical methods may be applied, e.g., CD analysis, to compare tertiary structure to other chemokines to evaluate whether the protein has likely folded into an active conformation. After transfection, a culture supernatant is collected and subjected to
15 bioassays. A mock control, e.g., a plasmid carrying the luciferase cDNA, is used. See, de Wet, et al. (1987) Mol. Cell. Biol. 7:725-757. A positive control, e.g., recombinant murine MIP-1 α from R&D Systems (Minneapolis, MN), is typically used. Likewise, antibodies may be used to block the biological
20 activities, e.g., as a control.

Lymphocyte migration assays are performed as previously described, e.g., in Bacon, et al. (1988) Br. J. Pharmacol. 95:966-974. Other trafficking assays are also available. See, e.g., Quidling-Järbrink, et al. (1995) Eur. J. Immunol. 25:322-327;
25 Koch, et al. (1994) J. Clinical Investigation 93:921-928; and Antony, et al. (1993) J. Immunol. 151:7216-7223. Murine Th2 T cell clones, CDC-25 (see Tony, et al. (1985) J. Exp. Med. 161:223-241) and HDK-1 (see Cherwinski, et al. (1987) J. Exp. Med. 166:1229-1244), made available from R. Coffman and A. O'Garra
30 (DNAX, Palo Alto, CA), respectively, are used as controls.

Ca²⁺ flux upon chemokine stimulation is measured according to the published procedure described in Bacon, et al. (1995) J. Immunol. 154:3654-3666.

Maximal numbers of migrating cells in response to MIP-1 α
35 typically occur at a concentration of 10⁻⁸ M, in agreement with

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original reports for CD4+ populations of human T cells. See Schall (1993) J. Exp. Med. 177:1821-1826. A dose-response curve is determined, preferably giving a characteristic bell shaped dose-response curve.

5 After stimulation with CC chemokines, lymphocytes generally show a measurable intracellular Ca²⁺ flux. MIP-1 α is capable of inducing immediate transients of calcium mobilization. Typically, the levels of chemokine used in these assays will be comparable to those used for the chemotaxis assays (1/1000 dilution of
10 conditioned supernatants).

XX. Biological Activities

A robust and sensitive assay is selected as described above, e.g., on immune cells, neuronal cells, or stem cells. Chemokine
15 is added to the assay in increasing doses to see if a dose response is detected. For example, in a proliferation assay, cells are plated out in plates. Appropriate culture medium is provided, and chemokine is added to the cells in varying amounts. Growth is monitored over a period of time which will detect either
20 a direct effect on the cells, or an indirect effect of the chemokine.

Alternatively, an activation assay or attraction assay is used. An appropriate cell type is selected, e.g., hematopoietic cells, myeloid (macrophages, neutrophils, polymorphonuclear cells,
25 etc.) or lymphoid (T cell, B cell, or NK cells), neural cells (neurons, neuroglia, oligodendrocytes, astrocytes, etc.), or stem cells, e.g., progenitor cells which differentiate to other cell types, e.g., gut crypt cells and undifferentiated cell types.

Retroviral infection assays have also been described using,
30 e.g., the CCR1, CCR3, and CCR5 receptors. These receptors, which bind the RANTES and MIP-1 related chemokines, are likely also to be receptors for the HCC5. Recent description of these chemokine receptors in retroviral infection processes, and the effects by the related RANTES and MIP-1 chemokines, suggest similar effects
35 may exist with the HCC5. See, e.g., Balter (1996) Science 272:1740 (describing evidence for chemokine receptors as coreceptors for HIV); and Deng, et al. (1996) Nature 381:661-666.

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Chemokines may also be assayed for activity in hemopoietic assays as described, e.g., by H. Broxmeyer. See Bellido, et al. (1995) J. Clinical Investigation 95:2886-2895; and Jilka, et al. (1995) Expt'l Hematology 23:500-506. They may be assayed for angiogenic activities as described, e.g., by Streiter, et al. (1992) Am. J. Pathol. 141:1279-1284. Or for a role in inflammation. See, e.g., Wakefield, et al. (1996) J. Surgical Res. 64:26-31.

Other assays will include those which have been demonstrated with other chemokines. See, e.g., Schall and Bacon (1994) Current Opinion in Immunology 6:865-873; and Bacon and Schall (1996) Int. Arch. Allergy & Immunol. 109:97-109.

The DUB genes will be screened for the deubiquitinating activities, as described. See, e.g., Hochstrasser (1995) Curr. Opin. Cell Biol. 7:215-223; Wilkinson, et al. (1995) Biochemistry 34:14535-14546; Baker, et al. (1992) J. Biol. Chem. 267:23364-23375; Baek et al. (1998) J. Biol. Chem. 272:25560-25565; and Papa and Hochstrasser (1993) Nature 366:313-319. For example, for an in vitro assay for UBP Activity, ^{125}I -labeled Ub-PESTc is used as a substrate according to the method of Woo, et al. (1995) J. Biol. Chem. 270:18766-18773. Reaction mixtures (0.1 ml) contain the proper amount of the enzyme preparations and 10-30 μg of ^{125}I -labeled Ub-PESTc in 100 mM Tris-HCl (pH 7.8), 1 mM dithiothreitol, 1 mM EDTA, and 5% glycerol. After incubating the mixtures for appropriate periods, the reaction is terminated by adding 50 μl of 40% (w/v) trichloroacetic acid and 50 μl of 1.2% (w/v) bovine serum albumin. The samples are centrifuged, and the resulting supernatants are counted for their radioactivities using a counter. The enzyme activity is expressed as a percentage of ^{125}I -labeled Ub-PESTc hydrolyzed to acid-soluble products. When assaying the hydrolysis of Ub-NH-carboxyl extension proteins and His-di-Ub, incubations are performed as above but in the presence of 5 μg of the substrate. After incubation for appropriate periods, the samples are subjected to discontinuous gel electrophoresis as described by Baek, et al. (1998) J. Biol. Chem.

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272:25560-25565. Proteins in the gels were then visualized by staining with Coomassie Blue R-250 or by exposing to x-ray films (Fuji) at 70° C. To prepare ¹²⁵I-labeled poly-Ub-NH-lysozyme conjugates, 2 µg of the ¹²⁵I-labeled lysozyme (5 x 10⁵ cpm) are
5 incubated with 10 µg of Ub, 120 µg of fraction II, and an ATP-regenerating system consisting of 10 mM Tris-HCl (pH 7.8), 15 units/ml creatine phosphokinase, 6.5 mM phosphocreatine, 1.5 mM ATP, 1 mM dithiothreitol, 0.5 mM MgCl₂, and 1 mM KCl in a final volume of 0.05 ml. Incubations are performed for 2 h at 37° C in
10 the presence of 1 mM hemin to prevent proteolysis of the ubiquitinated protein conjugates by the 26 S proteasome. After incubation, the samples are heated for 10 min at 55° C for inactivation of endogenous UBPs. Alternatively, Dub11 or Dub12 can be expressed as a GST fusion protein according to the method
15 of Zhu, et al. (1997) J. Biol. Chem. 272:51-57 by cloning into an appropriate expression vector and subsequently co-transformed with a plasmid encoding Ub-Met-β-gal, in which ubiquitin is fused to the NH₂ terminus of β-galactosidase and testing for cleavage.

However, the deubiquitinating enzymes have also been reported
20 to have additional functions besides deubiquitination. See, e.g., Hochstrasser (1996) Cell 84:813-815; Hicke and Riezman (1996) Cell 84:277-287; and Chen, et al. (1996) Cell 84:853-862.

The MD gene products will be screened for cell signaling activities. See, e.g., Miyake, et al. (1998) J. Immunol.
25 161:1348-1353; Kobe and Deisenhofer (1994) Trends Biochem. Sci. 19:412.

XXI. Antagonizing cyclin E2 proteins

The inhibition of cell cycle progression is especially
30 important for the control of abnormally proliferative diseases, e.g., cancer. Several methods are available to accomplish this control. The ability of cyclin binding is inhibited by the use, e.g., of antibodies raised against the cyclin binding proteins. Other elements include, e.g., peptidomimetics which are peptides
35 designed to mimic the binding site of cyclin associated proteins and disrupt the interaction of these proteins with cyclin. The

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most effective method to block cell cycle progression is the use of small molecules, e.g., to block the interaction of the associated proteins with cyclin, or to block downstream activity of the associated proteins, as described, e.g., in Hung, et al.

5 (1996) Chemistry and Biology 3:623-639. Exposure of a cell to these permeable small molecules should cause a conditional loss of function of the target protein.

Also included in this category is the use of gene therapy to block the expression of the cyclin associated protein or gene
10 transcription factors. Methods of using gene therapy are described, e.g., in Goodnow (1992) "Transgenic Animals" in Roitt (ed.) Encyclopedia of Immunology, Academic Press, San Diego, pp. 1502-1504; Travis (1992) Science 256:1392-1394; Kuhn, et al. (1991) Science 254:707-710; Capecchi (1989) Science 244:1288;
15 Robertson (1987) (ed.) Teratocarcinomas and Embryonic Stem Cells: A Practical Approach, IRL Press, Oxford; and Rosenberg (1992) J. Clinical Oncology 10:180-199. Also included is the use of antisense RNA in gene therapy to block expression of the target gene, or proper splicing of gene transcripts.

20 All citations herein are incorporated herein by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

25 Many modifications and variations of this invention can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. The specific embodiments described herein are offered by way of example only, and the invention is to be limited by the terms of the appended claims,
30 along with the full scope of equivalents to which such claims are entitled.

WHAT IS CLAIMED IS:

1. An isolated or recombinant antigenic polypeptide comprising:

- 5 a) a plurality of distinct segments, wherein each said segment has identity to at least 12 contiguous amino acids from the mature SEQ ID NO: 2; or
- b) at least 17 contiguous amino acids from the mature SEQ ID NO: 2.

10 2. The polypeptide of Claim 1, wherein said plurality of segments includes

- a) one of at least 19 contiguous amino acids; or
- b) two of at least 15 contiguous amino acids.

15 3. The polypeptide of Claim 1, wherein said polypeptide:

- a) comprises the mature SEQ ID NO: 2;
- b) binds with specificity to a polyclonal antibody which specifically binds to SEQ ID NO: 2; or
- 20 c) said polypeptide:
- i) is a natural allelic variant of SEQ ID NO: 2;
- ii) is at least 30 amino acids in length;
- iii) exhibits at least two non-overlapping epitopes specific for SEQ ID NO: 2;
- 25 iv) is a synthetic polypeptide;
- v) is attached to a solid substrate; or
- vi) is a 5-fold or less conservative substitution from SEQ ID NO: 2.

30 4. A fusion protein comprising first and second portions, said first portion comprising a polypeptide of Claim 1 and said second portion comprising a detectable marker.

5. A pharmaceutical composition comprising a sterile

35 polypeptide of Claim 1 in a pharmaceutically acceptable carrier.

6. An isolated or recombinant polynucleotide encoding a polypeptide of Claim 1.

7. The polynucleotide of Claim 6, which:

- a) comprises the mature polypeptide coding portion of SEQ ID NO: 1; or
5 b) encodes the mature SEQ ID NO: 2.

8. The polynucleotide of Claim 6, wherein said polynucleotide is:

- 10 a) a PCR product;
b) a hybridization probe;
c) a mutagenesis primer; or
d) made by chemical synthesis.

9. The polynucleotide of Claim 6, which is:

- 15 a) detectably labeled;
b) a deoxyribonucleic acid; or
c) double stranded.

10. An expression vector comprising a polynucleotide of
20 Claim 6.

11. The vector of Claim 10, wherein said polypeptide specifically binds polyclonal antibodies generated against an immunogen of mature SEQ ID NO: 2.

25

12. The vector of Claim 10, which

- a) selectively hybridizes under stringent hybridization conditions to a target polynucleotide sequence having at least 60 contiguous nucleotides from SEQ ID NO: 1;
30 b) encodes a polypeptide having at least 50 contiguous amino acid residues from mature SEQ ID NO: 2; or
c) is suitable for transfection into a prokaryote or eukaryote host cell.

35 13. The vector of Claim 12, wherein said host cell is:

- a) a mammalian cell;
b) a bacterial cell;

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- c) an insect cell;
- d) a prokaryote;
- e) a eukaryote; or
- f) a COS cell.

5

14. A method of making a polypeptide comprising expressing said vector of Claim 13 in said host cell.

10 15. An isolated or recombinant polynucleotide which hybridizes to the coding portion of SEQ ID NO: 1 under stringent hybridization and wash conditions of at least 50° C, a salt concentration of less than 400 mM, and 50% formamide.

15 16. An expression vector comprising the polynucleotide of Claim 15.

20 17. The vector of Claim 16 which hybridizes to the coding portion of SEQ ID NO: 1 under stringent hybridization and wash conditions of at least 60° C, a salt concentration of less than 200 mM, and 50% formamide.

25 18. The vector of Claim 25, which encodes a polypeptide which specifically binds an antibody generated against a mature SEQ ID NO: 2.

19. The polynucleotide of Claim 15 which hybridizes to SEQ ID NO: 1, wherein said polynucleotide is:

- a) a PCR product;
- b) a hybridization probe;
- 30 c) a mutagenesis primer; or
- d) made by chemical synthesis.

20. A method of modulating the physiology or development of a cell, comprising contacting said cell with an agonist or
35 antagonist of a polypeptide of Claim 1.

21. A method of detecting the presence of a complementary polynucleotide in a sample, comprising contacting a polynucleotide of Claim 6 that selectively hybridizes with said complementary polynucleotide in said sample to form a detectable duplex; thereby
5 indicating the presence of said polynucleotide in said sample.

22. A method for identifying a compound that binds to a polypeptide of Claim 1, comprising:

- 10 a) incubating components comprising said compound and said polypeptide under conditions sufficient to allow the components to interact; and
b) measuring the binding of the compound to said polypeptide.

15 23. An isolated or recombinant polynucleotide encoding an antigenic polypeptide comprising:

- 20 a) at least 17 contiguous amino acids from the mature polypeptide from SEQ ID NO: 6;
b) at least 17 contiguous amino acids from the mature polypeptide from SEQ ID NO: 8;
c) at least 17 contiguous amino acids from the mature polypeptide from SEQ ID NO: 10;
d) at least 17 contiguous amino acids from the mature polypeptide from SEQ ID NO: 12;
25 e) at least 17 contiguous amino acids from the mature polypeptide from SEQ ID NO: 17;
f) at least 17 contiguous amino acids from the mature polypeptide from SEQ ID NO: 19;
g) at least 17 contiguous amino acids from the mature polypeptide from SEQ ID NO: 21; or
30 h) at least 17 contiguous amino acids from the mature polypeptide from SEQ ID NO: 23.

24. The polynucleotide of Claim 23, encoding all of the polypeptide of:

- 35 a) signal processed SEQ ID NO: 6;
b) signal processed SEQ ID NO: 8;
c) signal processed SEQ ID NO: 10;

- d) signal processed SEQ ID NO: 12;
- e) signal processed SEQ ID NO: 17;
- f) SEQ ID NO: 19;
- g) SEQ ID NO: 21; or
- h) SEQ ID NO: 23.

25. The polynucleotide of Claim 23, which hybridizes at 55° C, less than 500 mM salt, and 50% formamide to the:

- a) mature protein coding portion of SEQ ID NO: 5;
- b) signal processed coding portion of SEQ ID NO: 7;
- c) signal processed coding portion of SEQ ID NO: 9;
- d) signal processed coding portion of SEQ ID NO: 11;
- e) mature protein coding portion of SEQ ID NO: 16;
- f) polypeptide coding portion of SEQ ID NO: 18;
- g) polypeptide coding portion of SEQ ID NO: 20; or
- h) polypeptide coding portion of SEQ ID NO: 22.

26. The polynucleotide of Claim 25, comprising at least 35 contiguous nucleotides of:

- a) mature protein coding portion of SEQ ID NO: 5;
- b) signal processed coding portion of SEQ ID NO: 7;
- c) signal processed coding portion of SEQ ID NO: 9;
- d) signal processed coding portion of SEQ ID NO: 11;
- e) mature protein coding portion of SEQ ID NO: 16;
- f) polypeptide coding portion of SEQ ID NO: 18;
- g) polypeptide coding portion of SEQ ID NO: 20; or
- h) polypeptide coding portion of SEQ ID NO: 22.

27. An expression vector comprising the polynucleotide of Claim 23.

28. A host cell containing the expression vector of Claim 27, including a eukaryotic cell.

29. A method of making an antigenic polypeptide comprising expressing a recombinant polynucleotide of Claim 23.

30. A method for detecting a polynucleotide of Claim 23, comprising contacting said polynucleotide with a probe that hybridizes, under stringent conditions, to at least 25 contiguous nucleotides of the:

- 5 a) mature protein coding portion of SEQ ID NO: 5;
 - b) signal processed coding portion of SEQ ID NO: 7;
 - c) signal processed coding portion of SEQ ID NO: 9;
 - d) signal processed coding portion of SEQ ID NO: 11;
 - e) mature protein coding portion of SEQ ID NO: 16;
 - 10 f) polypeptide coding portion of SEQ ID NO: 18;
 - g) polypeptide coding portion of SEQ ID NO: 20; or
 - h) polypeptide coding portion of SEQ ID NO: 22;
- to form a duplex, wherein detection of said duplex indicates the presence of said polynucleotide.

15 31. A kit for the detection of a polynucleotide of Claim 23, comprising a compartment containing a probe that hybridizes, under stringent hybridization conditions, to at least 17 contiguous nucleotides of a polynucleotide of Claim b1 to form a duplex.

20 32. The kit of Claim 31, wherein said probe is detectably labeled.

25 33. A binding compound comprising an antibody binding site which specifically binds to a polypeptide comprising at least 17 contiguous amino acids from:

- 30 a) signal processed SEQ ID NO: 6;
- b) signal processed SEQ ID NO: 8;
- c) signal processed SEQ ID NO: 10;
- d) signal processed SEQ ID NO: 12;
- e) signal processed SEQ ID NO: 17;
- f) SEQ ID NO: 19;
- g) SEQ ID NO: 21; or
- h) SEQ ID NO: 23.

35 34. The binding compound of Claim 33, wherein:
a) said antibody binding site is:

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- 1) selectively immunoreactive with the:
- a) signal processed SEQ ID NO: 6;
 - b) signal processed SEQ ID NO: 8;
 - c) signal processed SEQ ID NO: 10;
 - d) signal processed SEQ ID NO: 12;
 - e) signal processed SEQ ID NO: 17;
 - f) SEQ ID NO: 19;
 - g) SEQ ID NO: 21; or
 - h) SEQ ID NO: 23;
- 2) raised against a purified or recombinantly produced human HDTEA84 protein;
- 3) raised against a purified or recombinantly produced human HSLJD37R protein; or
- 4) in a monoclonal antibody, Fab, or F(ab)2; or
- b) said binding compound is:
- 1) an antibody molecule;
 - 2) a polyclonal antiserum;
 - 3) detectably labeled;
 - 4) sterile; or
 - 5) in a buffered composition.

35. A method using the binding compound of Claim 33, comprising contacting said binding compound with a biological sample comprising an antigen, thereby forming a binding compound:antigen complex.

36. The method of Claim 35, wherein said biological sample is from a human, and wherein said binding compound is an antibody.

37. A detection kit comprising said binding compound of Claim 34, and:

- a) instructional material for the use of said binding compound for said detection; or
- b) a compartment providing segregation of said binding compound.

38. A substantially pure or isolated antigenic polypeptide, which binds to said binding composition of Claim 33, and further comprises at least 17 contiguous amino acids from:

- a) signal processed SEQ ID NO: 6;
- 5 b) signal processed SEQ ID NO: 8;
- c) signal processed SEQ ID NO: 10;
- d) signal processed SEQ ID NO: 12;
- e) signal processed SEQ ID NO: 17;
- f) SEQ ID NO: 19;
- 10 g) SEQ ID NO: 21; or
- h) SEQ ID NO: 23.

39. The polypeptide of Claim 38, which:

- a) comprises at least a fragment of at least 25 contiguous
15 amino acid residues from a primate HDTEA84 protein;
- b) comprises at least a fragment of at least 25 contiguous
amino acid residues from a primate HSLJD37R protein;
- c) comprises at least a fragment of at least 25 contiguous
20 amino acid residues from a rodent or primate RANKL
protein;
- d) is a soluble polypeptide;
- e) is detectably labeled;
- f) is in a sterile composition;
- g) is in a buffered composition;
- 25 h) binds to an sialic acid residue;
- i) is recombinantly produced, or
- j) has a naturally occurring polypeptide sequence.

40. The polypeptide of Claim 39, which comprises at least 17 contiguous amino acids from the:

- 30 a) signal processed SEQ ID NO: 6;
- b) signal processed SEQ ID NO: 8;
- c) signal processed SEQ ID NO: 10;
- d) signal processed SEQ ID NO: 12;
- e) signal processed SEQ ID NO: 17;
- 35 f) SEQ ID NO: 19;
- g) SEQ ID NO: 21; or
- h) SEQ ID NO: 23.

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41. A method of modulating a precursor cell physiology or function comprising a step of contacting said cell with:

- a) a binding compound which binds to said polypeptide of Claim 38;
- b) an HDTEA84 polypeptide;
- c) an HSLJD37R polypeptide; or
- d) a RANKL polypeptide.

42. The method of Claim 41, wherein said contacting is in combination with a TNF family ligand, or an antagonist of said TNF family ligand.

43. A composition of matter selected from:

- a) a substantially pure or recombinant HCC5 polypeptide exhibiting identity over a length of at least 12 amino acids to SEQ ID NO: 25;
- b) an isolated natural sequence HCC5 of mature SEQ ID NO: 25;
- c) a fusion protein comprising HCC5 sequence;
- d) a substantially pure or recombinant Dub11 polypeptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 32 or 34;
- e) an isolated natural sequence Dub11 of mature SEQ ID NO: 32 or 34;
- f) a fusion protein comprising Dub11 sequence;
- g) a substantially pure or recombinant Dub12 polypeptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 36 or 38;
- h) an isolated natural sequence Dub12 of mature SEQ ID NO: 36 or 38;
- i) a fusion protein comprising Dub12 sequence;
- j) a substantially pure or recombinant MD-1 polypeptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 42;
- k) an isolated natural sequence MD-1 of mature SEQ ID NO: 42;

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- 1) a fusion protein comprising primate MD-1 sequence;
m) a substantially pure or recombinant MD-2 polypeptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 44 or 46;
5 n) an isolated natural sequence MD-2 of mature SEQ ID NO: 44 or 46;
o) a fusion protein comprising primate MD-2 sequence;
p) a substantially pure or recombinant MD-2 polypeptide exhibiting identity over a length of at least about 12
10 amino acids to SEQ ID NO: 48 or 49;
q) an isolated natural sequence MD-2 of mature SEQ ID NO: 48; or
r) a fusion protein comprising murine MD-2 sequence.
- 15 44. The composition of Claim 43, which is a substantially pure or isolated:
a) a HCC5 polypeptide, wherein said length is at least 17 amino acids;
b) a Dub11 polypeptide, wherein said length is at least 17
20 amino acids;
c) a Dub12 polypeptide, wherein said length is at least 17 amino acids;
d) a primate MD-1 polypeptide, wherein said length is at least 17 amino acids;
25 e) a primate MD-2 polypeptide, wherein said length is at least 17 amino acids; or
f) a rodent MD-2 polypeptide, wherein said length is at least 17 amino acids.
- 30 45. The composition of Claim 44, which is a substantially pure or isolated:
a) a HCC5 polypeptide, wherein said length is at least 21 amino acids;
b) a Dub11 polypeptide, wherein said length is at least 21
35 amino acids;
c) a Dub12 polypeptide, wherein said length is at least 21 amino acids;

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- d) a primate MD-1 polypeptide, wherein said length is at least 21 amino acids;
- e) a primate MD-2 polypeptide, wherein said length is at least 21 amino acids; and
- 5 f) a rodent MD-2 polypeptide, wherein said length is at least 21 amino acids.

46. The composition of matter of Claim 43, wherein said:

a) HCC5 polypeptide:

- 10 i) is from a primate, including a human;
- ii) comprises at least one polypeptide segment of SEQ ID NO: 25;
- iii) exhibits a plurality of portions exhibiting said identity;
- 15 iv) is a natural allelic variant of HCC5;
- v) has a length at least about 30 amino acids;
- vi) exhibits at least two non-overlapping epitopes which are specific for a primate HCC5;
- vii) exhibits a sequence identity over a length of at least 35 amino acids to a HCC5;
- 20 viii) is glycosylated;
- ix) is a synthetic polypeptide;
- x) is attached to a solid substrate;
- xi) is conjugated to another chemical moiety;
- 25 xii) is a 5-fold or less substitution from natural sequence; or
- xiii) is a deletion or insertion variant from a natural sequence;

b) Dub11 polypeptide:

- 30 i) is from a primate, including a human;
- ii) comprises at least one polypeptide segment of SEQ ID NO: 32 or 34;
- iii) exhibits a plurality of portions exhibiting said identity;
- 35 iv) is a natural allelic variant of Dub11;
- v) has a length at least about 30 amino acids;

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- vi) exhibits at least two non-overlapping epitopes which are specific for a primate Dub11;
- vii) exhibits a sequence identity over a length of at least about 35 amino acids to a Dub11;
- 5 viii) is glycosylated;
- ix) is a synthetic polypeptide;
- x) is attached to a solid substrate;
- xi) is conjugated to another chemical moiety;
- xii) is a 5-fold or less substitution from natural
- 10 sequence; or
- xiii) is a deletion or insertion variant from a natural sequence;
- c) Dub12 polypeptide:
- i) is from a primate, including a human;
- 15 ii) comprises at least one polypeptide segment of SEQ ID NO: 36 or 38;
- iii) exhibits a plurality of portions exhibiting said identity;
- iv) is a natural allelic variant of Dub12;
- 20 v) has a length at least about 30 amino acids;
- vi) exhibits at least two non-overlapping epitopes which are specific for a primate Dub12;
- vii) exhibits a sequence identity over a length of at least about 35 amino acids to a Dub12;
- 25 viii) is glycosylated;
- ix) is a synthetic polypeptide;
- x) is attached to a solid substrate;
- xi) is conjugated to another chemical moiety;
- xii) is a 5-fold or less substitution from natural
- 30 sequence; or
- xiii) is a deletion or insertion variant from a natural sequence;
- d) primate MD-1 polypeptide:
- i) is from a human;
- 35 ii) comprises at least one polypeptide segment of SEQ ID NO: 42;

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- iii) exhibits a plurality of portions exhibiting said identity;
- iv) is a natural allelic variant of primate MD-1;
- v) has a length at least about 30 amino acids;
- 5 vi) exhibits at least two non-overlapping epitopes which are specific for a primate MD-1;
- vii) exhibits a sequence identity over a length of at least about 35 amino acids to a primate MD-1;
- viii) is glycosylated;
- 10 ix) is a synthetic polypeptide;
- x) is attached to a solid substrate;
- xi) is conjugated to another chemical moiety;
- xii) is a 5-fold or less substitution from natural sequence; or
- 15 xiii) is a deletion or insertion variant from a natural sequence;
- e) primate MD-2 polypeptide::
 - i) is from a human;
 - ii) comprises at least one polypeptide segment of SEQ ID NO: 44 or 46;
 - 20 iii) exhibits a plurality of portions exhibiting said identity;
 - iv) is a natural allelic variant of primate MD-2;
 - v) has a length at least about 30 amino acids;
 - 25 vi) exhibits at least two non-overlapping epitopes which are specific for a primate MD-2;
 - vii) exhibits a sequence identity over a length of at least about 35 amino acids to a primate MD-2;
 - viii) is glycosylated;
 - 30 ix) is a synthetic polypeptide;
 - x) is attached to a solid substrate;
 - xi) is conjugated to another chemical moiety;
 - xii) is a 5-fold or less substitution from natural sequence; or
 - 35 xiii) is a deletion or insertion variant from a natural sequence; or
- f) rodent MD-2 polypeptide:

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- i) is from a mouse;
- ii) comprises at least one polypeptide segment of SEQ ID NO: 48 or 49;
- iii) exhibits a plurality of portions exhibiting said identity;
- iv) is a natural allelic variant of rodent MD-2;
- v) has a length at least about 30 amino acids;
- vi) exhibits at least two non-overlapping epitopes which are specific for a rodent MD-2;
- vii) exhibits a sequence identity over a length of at least about 35 amino acids to a rodent MD-2;
- viii) is glycosylated;
- ix) is a synthetic polypeptide;
- x) is attached to a solid substrate;
- xi) is conjugated to another chemical moiety;
- xii) is a 5-fold or less substitution from natural sequence; or
- xiii) is a deletion or insertion variant from a natural sequence.

47. A composition comprising a sterile polypeptide of Claim 43, wherein said polypeptide is:

- a) HCC5 polypeptide;
- b) Dub11 polypeptide;
- c) Dub12 polypeptide;
- d) MD-1 polypeptide; or
- e) MD-2 polypeptide.

48. A composition of Claim 43 comprising:

- a) said HCC5 polypeptide and:
 - 1) a carrier, wherein said carrier is:
 - a) an aqueous compound, including water, saline, and/or buffer; and/or
 - b) formulated for oral, rectal, nasal, topical, or parenteral administration;
 - 2) another chemokine, including one selected from the group of HCC1, HCC2, HCC3, and HCC4; or

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- 3) an antibody antagonist for a chemokine, including one selected from the group of HCC1, HCC2, HCC3, and HCC4;
- b) said Dub11 polypeptide and a carrier, wherein said carrier is
- a) an aqueous compound, including water, saline, and/or buffer; and/or
- b) formulated for oral, rectal, nasal, topical, or parenteral administration;
- c) said Dub12 polypeptide and a carrier, wherein said carrier is:
- a) an aqueous compound, including water, saline, and/or buffer; and/or
- b) formulated for oral, rectal, nasal, topical, or parenteral administration;
- d) said MD-1 polypeptide and a carrier, wherein said carrier is:
- a) an aqueous compound, including water, saline, and/or buffer; and/or
- b) formulated for oral, rectal, nasal, topical, or parenteral administration;
- e) said MD-2 polypeptide and a carrier, wherein said carrier is:
- a) an aqueous compound, including water, saline, and/or buffer; and/or
- b) formulated for oral, rectal, nasal, topical, or parenteral administration.

49. The fusion protein of Claim 43 comprising:

- a) mature protein sequence of Table 7;
- b) mature protein sequence of Table 9;
- b) mature protein sequence of Table 11;
- c) a detection or purification tag, including a FLAG, His6, or Ig sequence; or
- d) sequence of another chemokine protein with said protein in a).

50. A kit comprising a polypeptide of Claim 43, and:
- a) a compartment comprising said polypeptide; and/or
 - b) instructions for use or disposal of reagents in said kit.

5 51. A binding compound comprising an antigen binding portion from an antibody, which specifically binds to a natural:

- a) HCC5 polypeptide of Claim 43, wherein said antibody:
 - i) is raised against a peptide sequence of a mature polypeptide sequence of Table 7;
 - 10 ii) is raised against a mature HCC5;
 - iii) is raised to a purified HCC5;
 - iv) is immunoselected;
 - v) is a polyclonal antibody;
 - vi) binds to a denatured HCC5; or
 - 15 vii) exhibits a Kd to antigen of at least 30 μ M;
- b) Dub11 polypeptide of Claim 43, wherein said antibody:
 - i) is raised against a peptide sequence of a mature polypeptide sequence of Table 9;
 - ii) is raised against a mature Dub11;
 - 20 iii) is raised to a purified Dub11;
 - iv) is immunoselected;
 - v) is a polyclonal antibody;
 - vi) binds to a denatured Dub11; or
 - vii) exhibits a Kd to antigen of at least 30 μ M;
- 25 c) Dub12 polypeptide of Claim 43, wherein said antibody:
 - i) is raised against a peptide sequence of a mature polypeptide sequence of Table 9;
 - ii) is raised against a mature Dub12;
 - iii) is raised to a purified Dub12;
 - 30 iv) is immunoselected;
 - v) is a polyclonal antibody;
 - vi) binds to a denatured Dub12; or
 - vii) exhibits a Kd to antigen of at least 30 μ M;
- d) a primate MD-1 polypeptide of Claim 43, wherein said antibody:
- 35

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- i) is raised against a peptide sequence of a mature polypeptide sequence of Table 11;
ii) is raised against a mature MD-1;
iii) is raised to a purified MD-1;
5 iv) is immunoselected;
v) is a polyclonal antibody;
vi) binds to a denatured MD-1; or
vii) exhibits a Kd to antigen of at least 30 μ M;
- e) a primate MD-2 polypeptide of Claim 43, wherein said
10 antibody:
i) is raised against a peptide sequence of a mature polypeptide sequence of Table 11;
ii) is raised against a mature MD-2;
iii) is raised to a purified MD-2;
15 iv) is immunoselected;
v) is a polyclonal antibody;
vi) binds to a denatured MD-2; or
vii) exhibits a Kd to antigen of at least 30 μ M; or
- f) a rodent MD-2 polypeptide of Claim 43, wherein said
20 antibody:
i) is raised against a peptide sequence of a mature polypeptide sequence of Table 11;
ii) is raised against a mature rodent MD-2;
iii) is raised to a purified rodent MD-2;
25 iv) is immunoselected;
v) is a polyclonal antibody;
vi) binds to a denatured rodent MD-2; or
vii) exhibits a Kd to antigen of at least 30 μ M.
- 30 52. The binding composition of Claim 51, wherein:
a) said polypeptide is from a primate or rodent;
b) said binding compound is an Fv, Fab, or Fab2 fragment;
c) said binding compound is conjugated to another chemical moiety;
35 d) is attached to a solid substrate, including a bead or plastic membrane;

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- e) is in a sterile composition; or
- f) is detectably labeled, including a radioactive or fluorescent label.

- 5 53. A kit comprising said binding compound of Claim 51, and:
- a) a compartment comprising said binding compound;
 - b) a compartment comprising purified antigen; and/or
 - c) instructions for use or disposal of reagents in said kit.

- 10 54. A method of producing an antigen:antibody complex,
comprising contacting an antibody of Claim 51 and:
- a) a primate HCC5 polypeptide;
 - b) a primate Dub11 polypeptide;
 - c) a primate Dub12 polypeptide;
 - 15 d) a primate MD-1 polypeptide;
 - e) a primate MD-2 polypeptide; or
 - f) a rodent MD-2 polypeptide;
- thereby allowing said complex to form.

- 20 55. A composition comprising said binding compound of Claim
51 and:
- 1) a carrier, wherein said carrier is:
 - a) an aqueous compound, including water, saline, and/or
buffer; and/or
 - 25 b) formulated for oral, rectal, nasal, topical, or
parenteral administration; or
 - 2) an antibody antagonist for another chemokine, including
one selected from the group of HCC1, HCC2, HCC3, and
HCC4.

- 30 56. An isolated or recombinant nucleic acid encoding a
polypeptide or fusion protein of Claim 43, wherein:
- A) said HCC5 :
- a) polypeptide is from a primate, including a human; or
 - 35 b) nucleic acid:
 - i) encodes an antigenic HCC5 peptide sequence of Table
7;

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- ii) encodes a plurality of antigenic peptide sequences of Table 7;
- iii) exhibits identity over at least 25 nucleotides to a natural cDNA encoding said HCC5 segment;
- iv) is a hybridization probe for a gene encoding said HCC5 polypeptide; or
- v) further encodes another chemokine, including one selected from the group of HCC1, HCC2, HCC3, and HCC4;

10 B) said Dub11:

- a) polypeptide is from a primate, including a human; or
- b) nucleic acid:
 - i) encodes an antigenic Dub11 peptide sequence of Table 9;
 - ii) encodes a plurality of antigenic peptide sequences of Table 9;
 - iii) exhibits identity over at least 25 nucleotides to a natural cDNA encoding said Dub11 segment; or
 - iv) is a hybridization probe for a gene encoding said Dub11 polypeptide;

20 C) said Dub12:

- a) polypeptide is from a primate, including a human; or
- b) nucleic acid:
 - i) encodes an antigenic Dub12 peptide sequence of Table 9;
 - ii) encodes a plurality of antigenic peptide sequences of Table 9;
 - iii) exhibits identity over at least 25 nucleotides to a natural cDNA encoding said Dub12 segment;
 - iv) is a hybridization probe for a gene encoding said Dub12 polypeptide;

30 D) said primate MD-1:

- a) polypeptide is from a primate, including a human; or
- b) nucleic acid:
 - i) encodes an antigenic MD-1 peptide sequence of Table 11;

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- ii) encodes a plurality of antigenic peptide sequences of Table 11;
 - iii) exhibits identity over at least 25 nucleotides to a natural cDNA encoding said MD-1 segment;
 - 5 iv) is a hybridization probe for a gene encoding said Dub11 polypeptide;
- E) said primate MD-2:
- a) polypeptide is from a human; or
 - b) nucleic acid:
 - 10 i) encodes an antigenic MD-2 peptide sequence of Table 11;
 - ii) encodes a plurality of antigenic peptide sequences of Table 11;
 - 15 iii) exhibits identity over at least 25 nucleotides to a natural cDNA encoding said MD-2 segment;
 - iv) is a hybridization probe for a gene encoding said primate MD-2 polypeptide; or
- F) said rodent MD-2:
- a) polypeptide is from a mouse; or
 - 20 b) nucleic acid:
 - i) encodes an antigenic MD-2 peptide sequence of Table 11;
 - ii) encodes a plurality of antigenic peptide sequences of Table 11;
 - 25 iii) exhibits identity over at least 25 nucleotides to a natural cDNA encoding said MD-2 segment; or
 - iv) is a hybridization probe for a gene encoding said rodent MD-2 polypeptide.
- 30 57. The nucleic acid of Claim 56, which:
- a) is an expression vector;
 - b) further comprises an origin of replication;
 - c) is from a natural source;
 - d) comprises a detectable label;
 - 35 e) comprises synthetic nucleotide sequence;
 - f) is less than 6 kb, preferably less than 3 kb;
 - g) is from a primate, including a human;

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- h) comprises a natural full length coding sequence; or
- i) is a PCR primer, PCR product, or mutagenesis primer.

58. A cell or tissue comprising a recombinant nucleic acid
5 of Claim 56, including wherein said cell is:

- a) a prokaryotic cell;
- b) a eukaryotic cell;
- c) a bacterial cell;
- d) a yeast cell;
- 10 e) an insect cell;
- f) a mammalian cell;
- g) a mouse cell;
- h) a primate cell; or
- i) a human cell.

59. A kit comprising said nucleic acid of Claim 56, and:

- a) a compartment comprising said nucleic acid;
- b) a compartment comprising a nucleic acid encoding another chemokine, including HCC1, HCC2, HCC3, and HCC4; or
- 20 c) instructions for use or disposal of reagents in said kit.

60. A nucleic acid which:

- a) hybridizes under wash conditions of 45° C and less than 2M salt to the polypeptide coding portion of SEQ ID NO: 24;
- 25 b) hybridizes under wash conditions of 45° C and less than 2M salt to the polypeptide coding portions of SEQ ID NO: 31 or 33;
- c) hybridizes under wash conditions of 45° C and less than 2M salt to the coding portions of SEQ ID NO: 35 or 37;
- 30 d) hybridizes under wash conditions of 45° C and less than 2M salt to the coding portion of SEQ ID NO: 41;
- e) hybridizes under wash conditions of 45° C and less than 2M salt to the coding portion of SEQ ID NO: 43 or 45. or
- 35 f) hybridizes under wash conditions of 45° C and less than 2M salt to the coding portion of SEQ ID NO: 47.

61. The nucleic acid of Claim 57, wherein:

- a) said wash conditions are at 55° C and/or 500 mM salt; or
- b) said wash conditions are at 65° C and/or 150 mM salt.

5 62. A method of modulating physiology or development of a cell or tissue culture cells comprising exposing said cell to an agonist or antagonist of HCC5, primate MD-1, primate MD-2, or rodent MD-2.

10 63. A method of detecting specific binding to a compound, comprising:

- a) contacting said compound to a composition selected from the group of:
 - 15 i) an antigen binding site which specifically binds to a HCC5 chemokine;
 - ii) an antigen binding site which specifically binds to Dub11;
 - iii) an antigen binding site which specifically binds to Dub12;
 - 20 iv) an antigen binding site which specifically binds to primate MD-1;
 - v) an antigen binding site which specifically binds to primate MD-2;
 - vi) an antigen binding site which specifically binds to 25 rodent MD-2;
 - vii) an expression vector encoding a HCC5 chemokine or fragment thereof;
 - viii) an expression vector encoding a Dub11 or fragment thereof;
 - 30 ix) an expression vector encoding a Dub12 or fragment thereof;
 - x) an expression vector encoding a primate MD-1 or fragment thereof;
 - xi) an expression vector encoding a primate MD-2 or 35 fragment thereof;
 - xii) an expression vector encoding a rodent MD-2 or fragment thereof;

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- xiii) a substantially pure protein which is specifically recognized by said antigen binding site of (i);
- xiv) a substantially pure protein which is specifically recognized by said antigen binding site of (ii);
- xiv) a substantially pure protein which is specifically recognized by said antigen binding site of (iii);
- xiv) a substantially pure protein which is specifically recognized by said antigen binding site of (iv);
- xiv) a substantially pure protein which is specifically recognized by said antigen binding site of (v);
- xiv) a substantially pure protein which is specifically recognized by said antigen binding site of (vi);
- ix) a substantially pure HCC5 chemokine or peptide thereof of Claim 43, or a fusion protein comprising a 30 amino acid sequence portion of HCC5 chemokine sequence;
- x) a substantially pure Dub11 or peptide thereof of Claim 43, or a fusion protein comprising a 30 amino acid sequence portion of Dub11 sequence;
- xi) a substantially pure Dub12 or peptide thereof of Claim 43, or a fusion protein comprising a 30 amino acid sequence portion of Dub11 sequence;
- xi) a substantially pure primate MD-1 or peptide thereof of Claim 43, or a fusion protein comprising a 30 amino acid sequence portion of primate MD-1 sequence;
- xi) a substantially pure primate MD-2 or peptide thereof of Claim 43, or a fusion protein comprising a 30 amino acid sequence portion of primate MD-2 sequence;
- xi) a substantially pure rodent MD-2 or peptide thereof of Claim 43, or a fusion protein comprising a 30 amino acid sequence portion of rodent MD-2 sequence; and
- b) detecting binding of said compound to said composition.
64. An isolated or recombinant polynucleotide which:

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- a) encodes at least 17 contiguous amino acid residues of SEQ ID NO: 54;
- b) encodes at least two distinct segments of at least 10 contiguous amino acid residues of SEQ ID NO 54; or
- 5 c) comprises one or more segments at least 21 contiguous nucleotides of SEQ ID NO: 53.

65. A method of making:

- 10 a) a polypeptide comprising expressing an expression vector of Claim 64, thereby producing said polypeptide;
- b) a duplex nucleic acid comprising contacting a polynucleotide of Claim 64 with a complementary nucleic acid, thereby resulting in production of said duplex nucleic acid;
- 15 c) a synthetic polynucleotide of Claim 64, comprising chemically polymerizing nucleotides to produce said polynucleotide; or
- d) a polynucleotide of Claim 64 comprising using a PCR method.

20 66. An isolated or recombinant antigenic polypeptide comprising at least:

- a) one segment comprising at least 17 contiguous amino acids from SEQ ID NO: 54; or
- 25 b) at least two distinct segments of at least 11 contiguous amino acids from SEQ ID NO: 54.

67. The antigenic polypeptide of Claim 66, comprising at least one segment comprising at least 17 contiguous amino acids from SEQ ID NO: 54.

30

68. The polypeptide of Claim 66, which exhibits at least two non-overlapping epitopes which are selective for primate protein of SEQ ID NO: 54.

35 69. The polypeptide of Claim 66, wherein said polypeptide:

- a) is a 5-fold or less substitution from a natural sequence; or

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- b) is a deletion or insertion variant from a natural sequence.

70. A kit comprising said polypeptide of Claim 66, and instructions for the use or disposal of said polypeptide or other reagents of said kit.

71. The antigenic polypeptide of Claim 66, comprising at least two distinct segments of at least 11 contiguous amino acids from SEQ ID NO: 54.

72. The polypeptide of Claim 71:

- a) which comprises at least one sequence from (SEQ ID NO: 54) KESRYVHD (residues 120-127), DKHFEVLH (residues 127-134), HSDLEPQM (residues 134-141), QKDINKNM (residues 177-184), YAPKLQEF (residues 203-210), SEEDILRM (residues 219-226), LRMEIIL (residues 224-231), ELCPVTII (residues 237-244), and LFLQVDAL (residues 249-256); and/or
- b) wherein said segments of at least 11 contiguous amino acids comprise one said segment with at least 14 contiguous amino acids from SEQ ID NO: 54.

73. The polypeptide of Claim 71, which exhibits at least two non-overlapping epitopes which are selective for primate protein of SEQ ID NO: 54.

74. The polypeptide of Claim 71, wherein said polypeptide:

- a) comprises a mature sequence of SEQ ID NO: 2;
- b) binds with selectivity to an antibody generated against an immunogen of SEQ ID NO: 54;
- c) comprises a plurality of polypeptide segments of 17 contiguous amino acids of SEQ ID NO: 54; or
- d) is a natural allelic variant of SEQ ID NO: 54.

75. The polypeptide of Claim 71, wherein said polypeptide:

- a) is in a sterile composition;

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- b) has a length at least 30 amino acids;
- c) is not glycosylated;
- d) is denatured;
- e) is a synthetic polypeptide;
- 5 f) is attached to a solid substrate; or
- g) is a fusion protein with a detection or purification tag, including a FLAG, His6, or Ig sequence.

76. The polypeptide of Claim 71, wherein said
- 10 polypeptide:
- a) is a 5-fold or less substitution from a natural sequence; or
 - b) is a deletion or insertion variant from a natural sequence.

15 77. A kit comprising said polypeptide of Claim 71, and instructions for the use or disposal of said polypeptide or other reagents of said kit.

- 20 78. A method using said polypeptide of Claim 71:
- a) to label said polypeptide, comprising labeling said polypeptide with a radioactive label;
 - b) to separate said polypeptide from another polypeptide in a mixture, comprising running said mixture on a
 - 25 chromatography matrix, thereby separating said polypeptides;
 - c) to identify a compound that binds selectively to said polypeptide, comprising incubating said compound with said polypeptide under appropriate conditions; thereby
 - 30 causing said component to bind to said polypeptide; or
 - d) to conjugate said polypeptide to a matrix, comprising derivatizing said polypeptide with a reactive reagent, and conjugating said polypeptide to said matrix; or
 - e) inducing an antibody response to said polypeptide,
 - 35 comprising introducing said polypeptide as an antigen to an immune system, thereby inducing said response.

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79. A binding compound comprising an antigen binding portion from an antibody which binds with selectivity to a polypeptide of Claim 66.

5 80. A method of evaluating the selectivity of binding of a compound to cyclin E2, comprising contacting said compound to a recombinant cyclin E2 polypeptide and at least one other cyclin; and comparing binding of said compound to said cyclins.

10 81. The polypeptide of Claim 67:

a) which comprises at least one sequence from (SEQ ID NO: 54) KESRYVHD (residues 120-127), DKHFEVLH (residues 127-134), HSDLEPQM (residues 134-141), QKDINKNM (residues 177-184), YAPKLQEF (residues 203-210), SEEDILRM (residues 219-226), LRMEIIL (residues 224-231), ELCPVTII (residues 237-244), and LFLQVDAL (residues 249-256); and/or

b) wherein said segment comprising at least 17 contiguous amino acids exhibits at least 23 contiguous amino acids from SEQ ID NO: 54.

82. The polypeptide of Claim 67, wherein said polypeptide:

a) comprises a mature sequence of SEQ ID NO: 54;

b) binds with selectivity to an antibody generated against an immunogen of SEQ ID NO: 54;

c) comprises a plurality of polypeptide segments comprising at least 17 contiguous amino acids of SEQ ID NO: 54; or

d) is a natural allelic variant of SEQ ID NO: 54.

83. The polypeptide of Claim 67, wherein said polypeptide:

a) is in a sterile composition;

b) has a length at least 30 amino acids;

c) is not glycosylated;

d) is denatured;

e) is a synthetic polypeptide;

f) is attached to a solid substrate; or

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- g) is a fusion protein with a detection or purification tag, including a FLAG, His6, or Ig sequence.

84. A method using said polypeptide of Claim 67:

- 5 a) to label said polypeptide, comprising labeling said polypeptide with a radioactive label;
- b) to separate said polypeptide from another polypeptide in a mixture, comprising running said mixture on a chromatography matrix, thereby separating said polypeptides;
- 10 c) to identify a compound that binds selectively to said polypeptide, comprising incubating said compound with said polypeptide under appropriate conditions; thereby causing said component to bind to said polypeptide;
- 15 d) to conjugate said polypeptide to a matrix, comprising derivatizing said polypeptide with a reactive reagent, and conjugating said polypeptide to said matrix; or
- e) inducing an antibody response to said polypeptide, comprising introducing said polypeptide as an antigen to an immune system, thereby inducing said response.
- 20

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35	gtg ggt ggc gtc ctg gtc aag cgg ctc cac ctg ggc cct gtg gga tgc	1589
	Val Gly Gly Val Leu Val Lys Arg Leu His Leu Gly Pro Val Gly Cys	
	430 435 440	
40	ggt gcc ctt tgc ctg ctg ggg atg ctg ctg tgc ctc ttc ttc agc ctg	1637
	Gly Ala Leu Cys Leu Leu Gly Met Leu Leu Cys Leu Phe Phe Ser Leu	
	445 450 455	
45	ccg ctc ttc ttt atc ggc tgc tcc agc cac cag att gcg ggc atc aca	1685
	Pro Leu Phe Phe Ile Gly Cys Ser Ser His Gln Ile Ala Gly Ile Thr	
	460 465 470	
50	cac cag acc agt gcc cac cct ggg ctg gag ctg tct cca agc tgc atg	1733
	His Gln Thr Ser Ala His Pro Gly Leu Glu Leu Ser Pro Ser Cys Met	
	475 480 485 490	
55	gag gcc tgc tcc tgc cca ttg gac ggc ttt aac cct gtc tgc gac ccc	1781
	Glu Ala Cys Ser Cys Pro Leu Asp Gly Phe Asn Pro Val Cys Asp Pro	
	495 500 505	
60	agc act cgt gtg gaa tac atc aca ccc tgc cac gca ggc tgc tca agc	1829
	Ser Thr Arg Val Glu Tyr Ile Thr Pro Cys His Ala Gly Cys Ser Ser	
	510 515 520	
65	tgg gtg gtc cag gat gct ctg gac aac agc cag gtt ttc tac acc aac	1877
	Trp Val Val Gln Asp Ala Leu Asp Asn Ser Gln Val Phe Tyr Thr Asn	
	525 530 535	
70	tgc agc tgc gtg gtg gag ggc aac ccc gtg ctg gca gga tcc tgc gac	1925
	Cys Ser Cys Val Val Glu Gly Asn Pro Val Leu Ala Gly Ser Cys Asp	
	540 545 550	
75	tca acg tgc agc cat ctg gtg gtg ccc ttc ctg ctc ctg gtc agc ctg	1973
	Ser Thr Cys Ser His Leu Val Val Pro Phe Leu Leu Leu Val Ser Leu	
	555 560 565 570	

SUBSTITUTE SHEET (rule 26)

5	ggc tgc gcc ctg gcc tgt ctc acc cac aca ccc tcc ttc atg ctc atc Gly Ser Ala Leu Ala Cys Leu Thr His Thr Pro Ser Phe Met Leu Ile 575 580 585	2021
10	cta aga gga gtg aag aaa gaa gac aag act ttg gct gtg ggc atc cag Leu Arg Gly Val Lys Lys Glu Asp Lys Thr Leu Ala Val Gly Ile Gln 590 595 600	2069
15	ttc atg ttc ctg agg att ttg gcc tgg atg ccc agc ccc gtg atc cac Phe Met Phe Leu Arg Ile Leu Ala Trp Met Pro Ser Pro Val Ile His 605 610 615	2117
20	ggc agc gcc atc gac acc acc tgt gtg cac tgg gcc ctg agc tgt ggg Gly Ser Ala Ile Asp Thr Thr Cys Val His Trp Ala Leu Ser Cys Gly 620 625 630	2165
25	cgt cga gct gtc tgt cgc tac tac aat aat gac ctg ctc cga aac cgg Arg Arg Ala Val Cys Arg Tyr Tyr Asn Asn Asp Leu Leu Arg Asn Arg 635 640 645 650	2213
30	ttc atc ggc ctc cag ttc ttc ttc aaa aca ggt tct gtg atc tgc ttc Phe Ile Gly Leu Gln Phe Phe Phe Lys Thr Gly Ser Val Ile Cys Phe 655 660 665	2261
35	gcc tta gtt ttg gct gtc ctg agg cag cag gac aaa gag gca agg acc Ala Leu Val Leu Ala Val Leu Arg Gln Gln Asp Lys Glu Ala Arg Thr 670 675 680	2309
40	aaa gag agc aga tcc agc cct gcc gta gag cag caa ttg cta gtg tgc Lys Glu Ser Arg Ser Ser Pro Ala Val Glu Gln Gln Leu Leu Val Ser 685 690 695	2357
45	ggg cca ggg aag aag cca gag gat tcc cga gtg tgagctgtct tggggcccca Gly Pro Gly Lys Lys Pro Glu Asp Ser Arg Val 700 705	2410
50	cctggccaag agtagcagcc acagcagtac ctctcttgag tcctttgccc aagattgggt gtcaagagcc ctgtgttcca ttctggctcc tccactaaat tgctgtgtga cttcaggcaa gacattgatc ctctctcagc ctttgcttgc tagtctgaac caaagagttg tttgggcatt tgctgtgttg gccatttctg gagcaagagg gtcttcttcc tccttcccc agccagccag ctgtcctggg gccaggcttt cctgggtgga aagaagtata cctttccctg gggccctagg atagcaaagt gagccatagt gggccaggct gccctccatg ctggggcccca gccaggtct gcactcgcct ggatcacctt ctttgagcct tagccatctc ctgtcaggta ggaatgaact tgccagcctt caggctcgtt cagctatgac catctgtgcg gtcagggtac actcagctct cctccccaac tccagcagcc tttaagaagt gtccctttgg cgccccctgg aggcagagca ctgagctgga ccctgggtag actccacag ggaggacgga gctggcctca ggagtgggac accagactt ggcagggcct tcaagaggcc tgtgtggggg cccaggaat ccttagctga agcggggaga ctactctcc atctcaggaa attctagccc ttgccctcag ggagccacgg ttgagggtga ggccaacac ctgccttagg gccctgggtg ggcaagtctg ggccctgggg	2470 2530 2590 2650 2710 2770 2830 2890 2950 3010 3070 3130 3190

SUBSTITUTE SHEET (rule 26)

5 tagggaggga gactcaggcc cacacttggg tatttttctaa tttcagacaa acacacactc 3250
 agcgcgcact cactgattcc tacacattgc caagatttca cacatgtgac cagggggccac 3310
 caaagtccct gtgacctttg tgactaggat cctaatttct ctattttctc ctgggtgcct 3370
 10 ggggtctgtgt cacctggggc agtgtggata atgttttagtt ctgtgacact gttttttggg 3430
 ggtggcacct ggttctccga tgcctgggct ggtgtcaggc ccaggactgt agtgctggga 3490
 gcagtaaagc tcagctctgt gtaatgagt atgctatggc ttgctcgtgt cttatgatcc 3550
 15 aatccttttc tacatcagcc cttgttttgt tttatggcta gtcttatctg gcctggttat 3610
 ttccttgctg ggaggagagg gtttgcta atctgctcccag cccaacctat taccacccca 3670
 20 cctcgctggg acctactgct cgggaggcag cagacaggga gccaccagca gtggcttcct 3730
 ggccctgtgc tgggggtggg gggaagctgg gggcacatgt ggcccttgcc ttctgagcag 3790
 ctcccagtgc cagggctttg agactttccc acatgataaa agaaaaggga ggtacagaag 3850
 25 ttccaattcc ctttttattt tgctggttgg tatctgtaaa tgtttaataa atatctgagc 3910
 atgtatctat caacgccaag aatttcaaag tctccttcaa caatatgagg cttttaggat 3970
 30 gtttatattc cttcatccct cttgtttccc aggttttgca gggaaaaaag tctggaatta 4030
 tagatacagc ttattattaa atttgttctt gcat 4064

35 <210> 2
 <211> 709
 <212> PRT
 <213> Unknown
 40 <400> 2
 Met Gly Pro Arg Ile Gly Pro Ala Gly Glu Val Pro Gln Val Pro Asp
 1 5 10 15
 45 Lys Glu Thr Lys Ala Thr Met Gly Thr Glu Asn Thr Pro Gly Gly Lys
 20 25 30
 Ala Ser Pro Asp Pro Gln Asp Val Arg Pro Ser Val Phe His Asn Ile
 35 40 45
 50 Lys Leu Phe Val Leu Cys His Ser Leu Leu Gln Leu Ala Gln Leu Met
 50 55 60
 Ile Ser Gly Tyr Leu Lys Ser Ser Ile Ser Thr Val Glu Lys Arg Phe
 65 70 75 80
 55 Gly Leu Ser Ser Gln Thr Ser Gly Leu Leu Ala Ser Phe Asn Glu Val
 85 90 95
 60 Gly Asn Thr Ala Leu Ile Val Phe Val Ser Tyr Phe Gly Ser Arg Val
 100 105 110
 His Arg Pro Arg Met Ile Gly Tyr Gly Ala Ile Leu Val Ala Leu Ala
 115 120 125

SUBSTITUTE SHEET (rule 26)

5 Gly Leu Leu Met Thr Leu Pro His Phe Ile Ser Glu Pro Tyr Arg Tyr
 130 135 140
 Asp Asn Thr Ser Pro Glu Asp Met Pro Gln Asp Phe Lys Ala Ser Leu
 145 150 155 160
 10 Cys Leu Pro Thr Thr Ser Ala Pro Ala Ser Ala Pro Ser Asn Gly Asn
 165 170 175
 Cys Ser Ser Tyr Thr Glu Thr Gln His Leu Ser Val Val Gly Ile Met
 180 185 190
 Phe Val Ala Gln Thr Leu Leu Gly Val Gly Gly Val Pro Ile Gln Pro
 195 200 205
 20 Phe Gly Ile Ser Tyr Ile Asp Asp Phe Ala His Asn Ser Asn Ser Pro
 210 215 220
 Leu Tyr Leu Gly Ile Leu Phe Ala Val Thr Met Met Gly Pro Gly Leu
 225 230 235 240
 25 Ala Phe Gly Leu Gly Ser Leu Met Leu Arg Leu Tyr Val Asp Ile Asn
 245 250 255
 Gln Met Pro Glu Gly Gly Ile Ser Leu Thr Ile Lys Asp Pro Arg Trp
 260 265 270
 Val Gly Ala Trp Trp Leu Gly Phe Leu Ile Ala Ala Gly Ala Val Ala
 275 280 285
 35 Leu Ala Ala Ile Pro Tyr Phe Phe Phe Pro Lys Glu Met Pro Lys Glu
 290 295 300
 Lys Arg Glu Leu Gln Phe Arg Arg Lys Val Leu Ala Val Thr Asp Ser
 305 310 315 320
 40 Pro Ala Arg Lys Gly Lys Asp Ser Pro Ser Lys Gln Ser Pro Gly Glu
 325 330 335
 Ser Thr Lys Lys Gln Asp Gly Leu Val Gln Ile Ala Pro Asn Leu Thr
 340 345 350
 Val Ile Gln Phe Ile Lys Val Phe Pro Arg Val Leu Leu Gln Thr Leu
 355 360 365
 50 Arg His Pro Ile Phe Leu Leu Val Val Leu Ser Gln Val Cys Leu Ser
 370 375 380
 Ser Met Ala Ala Gly Met Ala Thr Phe Leu Pro Lys Phe Leu Glu Arg
 385 390 395 400
 55 Gln Phe Ser Ile Thr Ala Ser Tyr Ala Asn Leu Leu Ile Gly Cys Leu
 405 410 415
 Ser Phe Pro Ser Val Ile Val Gly Ile Val Val Gly Gly Val Leu Val
 420 425 430
 60 Lys Arg Leu His Leu Gly Pro Val Gly Cys Gly Ala Leu Cys Leu Leu
 435 440 445

SUBSTITUTE SHEET (rule 26)

5 Gly Met Leu Leu Cys Leu Phe Phe Ser Leu Pro Leu Phe Phe Ile Gly
 450 455 460
 Cys Ser Ser His Gln Ile Ala Gly Ile Thr His Gln Thr Ser Ala His
 465 470 475 480
 10 Pro Gly Leu Glu Leu Ser Pro Ser Cys Met Glu Ala Cys Ser Cys Pro
 485 490 495
 15 Leu Asp Gly Phe Asn Pro Val Cys Asp Pro Ser Thr Arg Val Glu Tyr
 500 505 510
 Ile Thr Pro Cys His Ala Gly Cys Ser Ser Trp Val Val Gln Asp Ala
 515 520 525
 20 Leu Asp Asn Ser Gln Val Phe Tyr Thr Asn Cys Ser Cys Val Val Glu
 530 535 540
 Gly Asn Pro Val Leu Ala Gly Ser Cys Asp Ser Thr Cys Ser His Leu
 545 550 555 560
 25 Val Val Pro Phe Leu Leu Leu Val Ser Leu Gly Ser Ala Leu Ala Cys
 565 570 575
 30 Leu Thr His Thr Pro Ser Phe Met Leu Ile Leu Arg Gly Val Lys Lys
 580 585 590
 Glu Asp Lys Thr Leu Ala Val Gly Ile Gln Phe Met Phe Leu Arg Ile
 595 600 605
 35 Leu Ala Trp Met Pro Ser Pro Val Ile His Gly Ser Ala Ile Asp Thr
 610 615 620
 Thr Cys Val His Trp Ala Leu Ser Cys Gly Arg Arg Ala Val Cys Arg
 625 630 635 640
 40 Tyr Tyr Asn Asn Asp Leu Leu Arg Asn Arg Phe Ile Gly Leu Gln Phe
 645 650 655
 Phe Phe Lys Thr Gly Ser Val Ile Cys Phe Ala Leu Val Leu Ala Val
 660 665 670
 45 Leu Arg Gln Gln Asp Lys Glu Ala Arg Thr Lys Glu Ser Arg Ser Ser
 675 680 685
 50 Pro Ala Val Glu Gln Gln Leu Leu Val Ser Gly Pro Gly Lys Lys Pro
 690 695 700
 Glu Asp Ser Arg Val
 705
 55
 <210> 3
 <211> 643
 <212> PRT
 <213> Unknown
 60
 <220>
 <223> Description of Unknown Organism:primate

SUBSTITUTE SHEET (rule 26)

<400> 3

5 Met Gly Leu Leu Pro Lys Leu Gly Val Ser Gln Gly Ser Asp Thr Ser
1 5 10 15

Thr Ser Arg Ala Gly Arg Cys Ala Arg Ser Val Phe Gly Asn Ile Lys
20 25 30

10 Val Phe Val Leu Cys Gln Gly Leu Leu Gln Leu Cys Gln Leu Leu Tyr
35 40 45

15 Ser Ala Tyr Phe Lys Ser Ser Leu Thr Thr Ile Glu Lys Arg Phe Gly
50 55 60

Leu Ser Ser Ser Ser Ser Gly Leu Ile Ser Ser Leu Asn Glu Ile Ser
65 70 75 80

20 Asn Ala Ile Leu Ile Ile Phe Val Ser Tyr Phe Gly Ser Arg Val His
85 90 95

Arg Pro Arg Leu Ile Gly Ile Gly Gly Leu Phe Leu Ala Ala Gly Ala
100 105 110

25 Phe Ile Leu Thr Leu Pro His Phe Leu Ser Glu Pro Tyr Gln Tyr Thr
115 120 125

30 Leu Ala Ser Thr Gly Asn Asn Ser Arg Leu Gln Ala Glu Leu Cys Gln
130 135 140

Lys His Trp Gln Asp Leu Pro Pro Ser Lys Cys His Ser Thr Thr Gln
145 150 155 160

35 Asn Pro Gln Lys Glu Thr Ser Ser Met Trp Gly Leu Met Val Val Ala
165 170 175

Gln Leu Leu Ala Gly Ile Gly Thr Val Pro Ile Gln Pro Phe Gly Ile
180 185 190

40 Ser Tyr Val Asp Asp Phe Ser Glu Pro Ser Asn Ser Pro Leu Tyr Ile
195 200 205

45 Ser Ile Leu Phe Ala Ile Ser Val Phe Gly Pro Ala Phe Gly Tyr Leu
210 215 220

Leu Gly Ser Ile Met Leu Gln Ile Phe Val Asp Tyr Gly Arg Val Asn
225 230 235 240

50 Thr Ala Ala Val Asn Leu Val Pro Gly Asp Pro Arg Trp Ile Gly Ala
245 250 255

Trp Trp Leu Gly Leu Leu Ile Ser Ser Ala Leu Leu Val Leu Thr Ser
260 265 270

55 Phe Pro Phe Phe Phe Phe Pro Arg Ala Met Pro Ile Gly Ala Lys Arg
275 280 285

60 Ala Pro Ala Thr Ala Asp Glu Ala Arg Lys Leu Glu Glu Ala Lys Ser
290 295 300

Arg Gly Ser Leu Val Asp Phe Ile Lys Arg Phe Pro Cys Ile Phe Leu
305 310 315 320

SUBSTITUTE SHEET (rule 26)

5 Arg Leu Leu Met Asn Ser Leu Phe Val Leu Val Val Leu Ala Gln Cys
 325 330 335
 Thr Phe Ser Ser Val Ile Ala Gly Leu Ser Thr Phe Leu Asn Lys Phe
 340 345 350
 10 Leu Glu Lys Gln Tyr Gly Thr Ser Ala Ala Tyr Ala Asn Phe Leu Ile
 355 360 365
 Gly Ala Val Asn Leu Pro Ala Ala Ala Leu Gly Met Leu Phe Gly Gly
 370 375 380
 15 Ile Leu Met Lys Arg Phe Val Phe Ser Leu Gln Thr Ile Pro Arg Ile
 385 390 395 400
 20 Ala Thr Thr Ile Ile Thr Ile Ser Met Ile Leu Cys Val Pro Leu Phe
 405 410 415
 Phe Met Gly Cys Ser Thr Pro Thr Val Ala Glu Val Tyr Pro Pro Ser
 420 425 430
 25 Thr Ser Ser Ser Ile His Pro Gln Ser Pro Ala Cys Arg Arg Asp Cys
 435 440 445
 Ser Cys Pro Asp Ser Ile Phe His Pro Val Cys Gly Asp Asn Gly Ile
 450 455 460
 30 Glu Tyr Leu Ser Pro Cys His Ala Gly Cys Ser Asn Ile Asn Met Ser
 465 470 475 480
 35 Ser Ala Thr Ser Lys Gln Leu Ile Tyr Leu Asn Cys Ser Cys Val Thr
 485 490 495
 Gly Gly Ser Ala Ser Ala Lys Thr Gly Ser Cys Pro Val Pro Cys Ala
 500 505 510
 40 His Phe Leu Leu Pro Ala Ile Phe Leu Ile Ser Phe Val Ser Leu Ile
 515 520 525
 Ala Cys Ile Ser His Asn Pro Leu Tyr Met Met Val Leu Arg Val Val
 530 535 540
 45 Asn Gln Glu Glu Lys Ser Phe Ala Ile Gly Val Gln Phe Leu Leu Met
 545 550 555 560
 50 Arg Leu Leu Ala Trp Leu Pro Ser Pro Ala Leu Tyr Gly Leu Thr Ile
 565 570 575
 Asp His Ser Cys Ile Arg Trp Asn Ser Leu Cys Leu Gly Arg Arg Gly
 580 585 590
 55 Ala Cys Ala Tyr Tyr Asp Asn Asp Ala Leu Arg Asp Arg Tyr Leu Gly
 595 600 605
 Leu Gln Met Gly Tyr Lys Ala Leu Gly Met Leu Leu Leu Cys Phe Ile
 610 615 620
 60 Ser Trp Arg Val Lys Lys Asn Lys Glu Tyr Asn Val Gln Lys Ala Ala
 625 630 635 640
 Gly Leu Ile

SUBSTITUTE SHEET (rule 26)

10

5 <210> 4
 <211> 643
 <212> PRT
 <213> Unknown

10 <220>
 <223> Description of Unknown Organism: rodent

<400> 4

15 Met Gly Leu Leu Leu Lys Pro Gly Ala Arg Gln Gly Ser Gly Thr Ser
 1 5 10 15

Ser Val Pro Asp Arg Arg Cys Pro Arg Ser Val Phe Ser Asn Ile Lys
 20 25 30

20 Val Phe Val Leu Cys His Gly Leu Leu Gln Leu Cys Gln Leu Leu Tyr
 35 40 45

Ser Ala Tyr Phe Lys Ser Ser Leu Thr Thr Ile Glu Lys Arg Phe Gly
 50 55 60

25 Leu Ser Ser Ser Ser Ser Gly Leu Ile Ser Ser Leu Asn Glu Ile Ser
 65 70 75 80

30 Asn Ala Thr Leu Ile Ile Phe Ile Ser Tyr Phe Gly Ser Arg Val Asn
 85 90 95

Arg Pro Arg Met Ile Gly Ile Gly Gly Leu Leu Leu Ala Ala Gly Ala
 100 105 110

35 Phe Val Leu Thr Leu Pro His Phe Leu Ser Glu Pro Tyr Gln Tyr Thr
 115 120 125

Ser Thr Thr Asp Gly Asn Arg Ser Ser Phe Gln Thr Asp Leu Cys Gln
 130 135 140

40 Lys His Phe Gly Ala Leu Pro Pro Ser Lys Cys His Ser Thr Val Pro
 145 150 155 160

45 Asp Thr His Lys Glu Thr Ser Ser Leu Trp Gly Leu Met Val Val Ala
 165 170 175

Gln Leu Leu Ala Gly Ile Gly Thr Val Pro Ile Gln Pro Phe Gly Ile
 180 185 190

50 Ser Tyr Val Asp Asp Phe Ala Glu Pro Thr Asn Ser Pro Leu Tyr Ile
 195 200 205

Ser Ile Leu Phe Ala Ile Ala Val Phe Gly Pro Ala Phe Gly Tyr Leu
 210 215 220

55 Leu Gly Ser Val Met Leu Arg Ile Phe Val Asp Tyr Gly Arg Val Asp
 225 230 235 240

60 Thr Ala Thr Val Asn Leu Ser Pro Gly Asp Pro Arg Trp Ile Gly Ala
 245 250 255

Trp Trp Leu Gly Leu Leu Ile Ser Ser Gly Phe Leu Ile Val Thr Ser
 260 265 270

SUBSTITUTE SHEET (rule 26)

11

5	Leu	Pro	Phe	Phe	Phe	Phe	Pro	Arg	Ala	Met	Ser	Arg	Gly	Ala	Glu	Arg	275	280	285
	Ser	Val	Thr	Ala	Glu	Glu	Thr	Met	Gln	Thr	Glu	Glu	Asp	Lys	Ser	Arg	290	295	300
10	Gly	Ser	Leu	Met	Asp	Phe	Ile	Lys	Arg	Phe	Pro	Arg	Ile	Phe	Leu	Arg	305	310	315
	Leu	Leu	Met	Asn	Pro	Leu	Phe	Met	Leu	Val	Val	Leu	Ser	Gln	Cys	Thr	325	330	335
15	Phe	Ser	Ser	Val	Ile	Ala	Gly	Leu	Ser	Thr	Phe	Leu	Asn	Lys	Phe	Leu	340	345	350
20	Glu	Lys	Gln	Tyr	Gly	Ala	Thr	Ala	Ala	Tyr	Ala	Asn	Phe	Leu	Ile	Gly	355	360	365
	Ala	Val	Asn	Leu	Pro	Ala	Ala	Ala	Leu	Gly	Met	Leu	Phe	Gly	Gly	Ile	370	375	380
25	Leu	Met	Lys	Arg	Phe	Val	Phe	Pro	Leu	Gln	Thr	Ile	Pro	Arg	Val	Ala	385	390	395
	Ala	Thr	Ile	Ile	Thr	Ile	Ser	Met	Ile	Leu	Cys	Val	Pro	Leu	Phe	Phe	405	410	415
30	Met	Gly	Cys	Ser	Thr	Ser	Ala	Val	Ala	Glu	Val	Tyr	Pro	Pro	Ser	Thr	420	425	430
35	Ser	Ser	Ser	Ile	His	Pro	Gln	Gln	Pro	Pro	Ala	Cys	Arg	Arg	Asp	Cys	435	440	445
	Ser	Cys	Pro	Asp	Ser	Phe	Phe	His	Pro	Val	Cys	Gly	Asp	Asn	Gly	Val	450	455	460
40	Glu	Tyr	Val	Ser	Pro	Cys	His	Ala	Gly	Cys	Ser	Ser	Thr	Asn	Thr	Ser	465	470	475
	Ser	Glu	Ala	Ser	Lys	Glu	Pro	Ile	Tyr	Leu	Asn	Cys	Ser	Cys	Val	Ser	485	490	495
45	Gly	Gly	Ser	Ala	Ser	Gln	Asp	Arg	Leu	Met	Pro	His	Val	Leu	Arg	Ala	500	505	510
50	Leu	Leu	Leu	Pro	Ser	Ile	Phe	Leu	Ile	Ser	Phe	Ala	Ala	Leu	Ile	Ala	515	520	525
	Cys	Ile	Ser	His	Asn	Pro	Leu	Tyr	Met	Met	Val	Leu	Arg	Val	Val	Asn	530	535	540
55	Gln	Asp	Glu	Lys	Ser	Phe	Ala	Ile	Gly	Val	Gln	Phe	Leu	Leu	Met	Arg	545	550	555
	Leu	Leu	Ala	Trp	Leu	Pro	Ala	Pro	Ser	Leu	Tyr	Gly	Leu	Leu	Ile	Asp	565	570	575
60	Ser	Ser	Cys	Val	Arg	Trp	Asn	Tyr	Leu	Cys	Ser	Gly	Arg	Arg	Gly	Ala	580	585	590

SUBSTITUTE SHEET (rule 26)

12

5 Cys Ala Tyr Tyr Asp Asn Asp Ala Leu Arg Asn Arg Tyr Leu Gly Leu
595 600 605

Gln Met Val Tyr Lys Ala Leu Gly Thr Leu Leu Leu Phe Phe Ile Ser
610 615 620

10 Trp Arg Met Lys Lys Asn Arg Glu Tyr Ser Leu Gln Glu Asn Thr Ser
625 630 635 640

Gly Leu Ile

15

<210> 5
<211> 1137
<212> DNA
20 <213> Unknown

<220>
<221> CDS
<222> (99)..(998)

25

<220>
<221> misc_difference
<222> (367)
<223> may be A; translation would be Asn

30

<220>
<223> Description of Unknown Organism:primate

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35 cgcaggcgga cccgggggcaa aggaggtggc atgtcgggtca ggcacagcag ggtcctgtgt 60

ccgcgctgag ccgcgctctc cctgctccag caaggacc atg agg gcg ctg gag ggg 116
Met Arg Ala Leu Glu Gly
1 5

40

cca ggc ctg tcg ctg ctg tgc ctg gtg ttg gcg ctg cct gcc ctg ctg 164
Pro Gly Leu Ser Leu Leu Cys Leu Val Leu Ala Leu Pro Ala Leu Leu
10 15 20

45

ccg gtg ccg gct gta cgc gga gtg gca gaa aca ccc acc tac ccc tgg 212
Pro Val Pro Ala Val Arg Gly Val Ala Glu Thr Pro Thr Tyr Pro Trp
25 30 35

50

cgg gac gca gag aca ggg gag cgg ctg gtg tgc gcc cag tgc ccc cca 260
Arg Asp Ala Glu Thr Gly Glu Arg Leu Val Cys Ala Gln Cys Pro Pro
40 45 50

55

ggc acc ttt gtg cag cgg ccg tgc cgc cga gac agc ccc atg acg tgt 308
Gly Thr Phe Val Gln Arg Pro Cys Arg Arg Asp Ser Pro Met Thr Cys
55 60 65 70

60

ggc ccg tgt cca ccg cgc cac tac acg cag ttc tgg aac tac ctg gag 356
Gly Pro Cys Pro Pro Arg His Tyr Thr Gln Phe Trp Asn Tyr Leu Glu
75 80 85

cgc tgc cgc tac tgc tac gtc ctc tgc ggg gag cgt gag gag gag gca 404
Arg Cys Arg Tyr Cys Tyr Val Leu Cys Gly Glu Arg Glu Glu Glu Ala
90 95 100

SUBSTITUTE SHEET (rule 26)

13

5	cgg gct tgc cac gcc acc cac aac cgt gcc tgc cgc tgc cgc acc ggc Arg Ala Cys His Ala Thr His Asn Arg Ala Cys Arg Cys Arg Thr Gly	452
	105 110 115	
10	ttc ttc gcg cac gct ggt ttc tgc ttg gag cac gca tgc tgt cca cct Phe Phe Ala His Ala Gly Phe Cys Leu Glu His Ala Ser Cys Pro Pro	500
	120 125 130	
15	ggt gcc ggc gtg att gcc ccg ggc acc ccc agc cag aac acg cag tgc Gly Ala Gly Val Ile Ala Pro Gly Thr Pro Ser Gln Asn Thr Gln Cys	548
	135 140 145 150	
	cag ccg tgc ccc cca ggc acc ttc tca gcc agc agc tcc agc tca gag Gln Pro Cys Pro Pro Gly Thr Phe Ser Ala Ser Ser Ser Ser Ser Glu	596
	155 160 165	
20	cag tgc cag ccc cac cgc aac tgc acg gcc ctg ggc ctg gcc ctc aat Gln Cys Gln Pro His Arg Asn Cys Thr Ala Leu Gly Leu Ala Leu Asn	644
	170 175 180	
25	gtg cca ggc tct tcc tcc cat gac acc ctg tgc acc agc tgc act ggc Val Pro Gly Ser Ser Ser His Asp Thr Leu Cys Thr Ser Cys Thr Gly	692
	185 190 195	
30	ttc ccc ctc agc acc agg gta cca gga gct gag gag tgt gag cgt gcc Phe Pro Leu Ser Thr Arg Val Pro Gly Ala Glu Glu Cys Glu Arg Ala	740
	200 205 210	
35	gtc atc gac ttt gtg gct ttc cag gac atc tcc atc aag agg ctg cag Val Ile Asp Phe Val Ala Phe Gln Asp Ile Ser Ile Lys Arg Leu Gln	788
	215 220 225 230	
	cgg ctg ctg cag gcc ctc gag gcc ccg gag ggc tgg ggt ccg aca cca Arg Leu Leu Gln Ala Leu Glu Ala Pro Glu Gly Trp Gly Pro Thr Pro	836
	235 240 245	
40	agg gcg ggc cgc gcg gcc ttg cag ctg aag ctg cgt cgg cgg ctc acg Arg Ala Gly Arg Ala Ala Leu Gln Leu Lys Leu Arg Arg Arg Leu Thr	884
	250 255 260	
45	gag ctc ctg ggg gcg cag gac ggg gcg ctg ctg gtg cgg ctg ctg cag Glu Leu Leu Gly Ala Gln Asp Gly Ala Leu Leu Val Arg Leu Leu Gln	932
	265 270 275	
50	gcg ctg cgc gtg gcc agg atg ccc ggg ctg gag cgg agc gtc cgt gag Ala Leu Arg Val Ala Arg Met Pro Gly Leu Glu Arg Ser Val Arg Glu	980
	280 285 290	
55	cgc ttc ctc cct gtg cac tgatcctggc cccctcttat ttattctaca Arg Phe Leu Pro Val His	1028
	295 300	
	tccttggcac cccacttgca ctgaaagagg ctttttttta aatagaagaa atgaggtttc	1088
	ttaaagctta tttttataaaa gctttttcat aaaaaaaaaa aaaaaaaaaa	1137
60	<210> 6 <211> 300 <212> PRT	

SUBSTITUTE SHEET (rule 26)

14

5 <213> Unknown
 <400> 6
 Met Arg Ala Leu Glu Gly Pro Gly Leu Ser Leu Leu Cys Leu Val Leu
 1 5 10 15
 10 Ala Leu Pro Ala Leu Leu Pro Val Pro Ala Val Arg Gly Val Ala Glu
 20 25 30
 Thr Pro Thr Tyr Pro Trp Arg Asp Ala Glu Thr Gly Glu Arg Leu Val
 35 40 45
 15 Cys Ala Gln Cys Pro Pro Gly Thr Phe Val Gln Arg Pro Cys Arg Arg
 50 55 60
 20 Asp Ser Pro Met Thr Cys Gly Pro Cys Pro Pro Arg His Tyr Thr Gln
 65 70 75 80
 Phe Trp Asn Tyr Leu Glu Arg Cys Arg Tyr Cys Tyr Val Leu Cys Gly
 85 90 95
 25 Glu Arg Glu Glu Glu Ala Arg Ala Cys His Ala Thr His Asn Arg Ala
 100 105 110
 Cys Arg Cys Arg Thr Gly Phe Phe Ala His Ala Gly Phe Cys Leu Glu
 115 120 125
 30 His Ala Ser Cys Pro Pro Gly Ala Gly Val Ile Ala Pro Gly Thr Pro
 130 135 140
 35 Ser Gln Asn Thr Gln Cys Gln Pro Cys Pro Pro Gly Thr Phe Ser Ala
 145 150 155 160
 Ser Ser Ser Ser Ser Glu Gln Cys Gln Pro His Arg Asn Cys Thr Ala
 165 170 175
 40 Leu Gly Leu Ala Leu Asn Val Pro Gly Ser Ser Ser His Asp Thr Leu
 180 185 190
 Cys Thr Ser Cys Thr Gly Phe Pro Leu Ser Thr Arg Val Pro Gly Ala
 195 200 205
 45 Glu Glu Cys Glu Arg Ala Val Ile Asp Phe Val Ala Phe Gln Asp Ile
 210 215 220
 50 Ser Ile Lys Arg Leu Gln Arg Leu Leu Gln Ala Leu Glu Ala Pro Glu
 225 230 235 240
 Gly Trp Gly Pro Thr Pro Arg Ala Gly Arg Ala Ala Leu Gln Leu Lys
 245 250 255
 55 Leu Arg Arg Arg Leu Thr Glu Leu Leu Gly Ala Gln Asp Gly Ala Leu
 260 265 270
 Leu Val Arg Leu Leu Gln Ala Leu Arg Val Ala Arg Met Pro Gly Leu
 275 280 285
 60 Glu Arg Ser Val Arg Glu Arg Phe Leu Pro Val His
 290 295 300

SUBSTITUTE SHEET (rule 26)

15

5 <210> 7
 <211> 1031
 <212> DNA
 <213> Unknown

 10 <220>
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 <222> (402)..(1031)

 15 <220>
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 aagcttcgct atgggaagtc gttcctttgc tctctcgcg ccagtcctcc tccctgggttc 120
 20 tcctcagccg ctgtcggagg agagcaccgc gagacgcggg ctgcagtcgc ggcggcttct 180
 ccccgccctgg gcggccgcgc cgctgggcag gtgctgagcg cccctagagc ctcccttgcc 240
 25 gcctccctcc tctgcccggc cgcagcagtg cacatggggg gttggaggta gatgggctcc 300
 cgccccggga ggcggcggtg gatgcggcgc tgggcagaag cagccgccga ttccagctgc 360
 30 cccgcgcgcc ccggggcgccc ctgcgagtc ccggttcagc c atg ggg acc tct ccg 416
 Met Gly Thr Ser Pro
 1 5

 agc agc agc acc gcc ctc gcc tcc tgc agc cgc atc gcc cgc cga gcc 464
 35 Ser Ser Ser Thr Ala Leu Ala Ser Cys Ser Arg Ile Ala Arg Arg Ala
 10 15 20

 aca gcc acg atg atc gcg ggc tcc ctt ctc ctg ctt gga ttc ctt agc 512
 Thr Ala Thr Met Ile Ala Gly Ser Leu Leu Leu Leu Gly Phe Leu Ser
 25 30 35
 40 acc acc aca gct cag cca gaa cag aag gcc tcg aat ctc att ggc aca 560
 Thr Thr Thr Ala Gln Pro Glu Gln Lys Ala Ser Asn Leu Ile Gly Thr
 40 45 50
 45 tac cgc cat gtt gac cgt gcc acc ggc cag gtg cta acc tgt gac aag 608
 Tyr Arg His Val Asp Arg Ala Thr Gly Gln Val Leu Thr Cys Asp Lys
 55 60 65

 tgt cca gca gga acc tat gtc tct gag cat tgt acc aac aca agc tgc 656
 50 Cys Pro Ala Gly Thr Tyr Val Ser Glu His Cys Thr Asn Thr Ser Cys
 70 75 80 85

 gcg tct ggc agc agt tgc cct gtg ggg acc ttt acc agg cat gag aat 704
 55 Ala Ser Gly Ser Ser Cys Pro Val Gly Thr Phe Thr Arg His Glu Asn
 90 95 100

 ggc ata gag aaa tgc cat gac tgt agt cag cca tgc cca tgg cca atg 752
 Gly Ile Glu Lys Cys His Asp Cys Ser Gln Pro Cys Pro Trp Pro Met
 105 110 115
 60 att gag aaa tta cct tgt gct gcc ttg act gac cga gaa tgc act tgc 800
 Ile Glu Lys Leu Pro Cys Ala Ala Leu Thr Asp Arg Glu Cys Thr Cys
 120 125 130

SUBSTITUTE SHEET (rule 26)

5	cca cct ggc atg ttc cag tct aac gct acc tgt gcc ccc cat acg gtg	848
	Pro Pro Gly Met Phe Gln Ser Asn Ala Thr Cys Ala Pro His Thr Val	
	135 140 145	
10	tgt cct gtg ggt tgg ggt gtg cgg aag aaa ggg aca gag act gag gat	896
	Cys Pro Val Gly Trp Gly Val Arg Lys Lys Gly Thr Glu Thr Glu Asp	
	150 155 160 165	
15	gtg cgg tgt aag cag tgt gct cgg ggg tac ttc tca gat gtg cct tct	944
	Val Arg Cys Lys Gln Cys Ala Arg Gly Tyr Phe Ser Asp Val Pro Ser	
	170 175 180	
20	agt gtg atg aac gca aag cat aca cag act gtc tgg atc aga acc tgg	992
	Ser Val Met Asn Ala Lys His Thr Gln Thr Val Trp Ile Arg Thr Trp	
	185 190 195	
25	ttg gtg atc aag ccg ggg gga cca agg aga cag aca act	1031
	Leu Val Ile Lys Pro Gly Gly Pro Arg Arg Gln Thr Thr	
	200 205 210	
30	<210> 8	
	<211> 210	
	<212> PRT	
	<213> Unknown	
35	<400> 8	
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	1 5 10 15	
40	Ile Ala Arg Arg Ala Thr Ala Thr Met Ile Ala Gly Ser Leu Leu Leu	
	20 25 30	
45	Leu Gly Phe Leu Ser Thr Thr Thr Ala Gln Pro Glu Gln Lys Ala Ser	
	35 40 45	
50	Asn Leu Ile Gly Thr Tyr Arg His Val Asp Arg Ala Thr Gly Gln Val	
	50 55 60	
55	Leu Thr Cys Asp Lys Cys Pro Ala Gly Thr Tyr Val Ser Glu His Cys	
	65 70 75 80	
60	Thr Asn Thr Ser Cys Ala Ser Gly Ser Ser Cys Pro Val Gly Thr Phe	
	85 90 95	
65	Thr Arg His Glu Asn Gly Ile Glu Lys Cys His Asp Cys Ser Gln Pro	
	100 105 110	
70	Cys Pro Trp Pro Met Ile Glu Lys Leu Pro Cys Ala Ala Leu Thr Asp	
	115 120 125	
75	Arg Glu Cys Thr Cys Pro Pro Gly Met Phe Gln Ser Asn Ala Thr Cys	
	130 135 140	
80	Ala Pro His Thr Val Cys Pro Val Gly Trp Gly Val Arg Lys Lys Gly	
	145 150 155 160	
85	Thr Glu Thr Glu Asp Val Arg Cys Lys Gln Cys Ala Arg Gly Tyr Phe	
	165 170 175	

SUBSTITUTE SHEET (rule 26)

17

5 Ser Asp Val Pro Ser Ser Val Met Asn Ala Lys His Thr Gln Thr Val
 180 185 190
 Trp Ile Arg Thr Trp Leu Val Ile Lys Pro Gly Gly Pro Arg Arg Gln
 195 200 205
 10 Thr Thr
 210
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 30 cctgggttctc ctcagccgct gtcggaggag agcaccgga gacgcgggct gcagtcgcgg 180
 cggcttctcc ccgcctgggc ggccgcgccc ctgggcaggt gctgagcgcc cctagcgcct 240
 35 cccttgccgc ctccctcctc tgcccggccg cagcagtgca catggggtgt tggaggtaga 300
 tgggctcccg gcccgggagg cggcggtgga tgcggcgctg ggcagaagca gccgccgatt 360
 40 ccagctgccc cgcgcgcccc gggcgcccct gcgagtcccc gggttcagcc atg ggg acc 418
 Met Gly Thr
 1
 tct ccg agc agc agc acc gcc ctc gcc tcc tgc agc cgc atc gcc cgc 466
 45 Ser Pro Ser Ser Ser Thr Ala Leu Ala Ser Cys Ser Arg Ile Ala Arg
 5 10 15
 cga gcc aca gcc acg atg atc gcg ggc tcc ctt ctc ctg ctt gga ttc 514
 Arg Ala Thr Ala Thr Met Ile Ala Gly Ser Leu Leu Leu Leu Gly Phe
 20 25 30 35
 50 ctt agc acc acc aca gct cag cca gaa cag aag gcc tcg aat ctc att 562
 Leu Ser Thr Thr Thr Ala Gln Pro Glu Gln Lys Ala Ser Asn Leu Ile
 40 45 50
 55 ggc aca tac cgc cat gtt gac cgt gcc acc ggc cag gtg cta acc tgt 610
 Gly Thr Tyr Arg His Val Asp Arg Ala Thr Gly Gln Val Leu Thr Cys
 55 60 65
 60 gac aag tgt cca gca gga acc tat gtc tct gag cat tgt acc aac aca 658
 Asp Lys Cys Pro Ala Gly Thr Tyr Val Ser Glu His Cys Thr Asn Thr
 70 75 80

SUBSTITUTE SHEET (rule 26)

18

5	agc ctg cgc gtc tgc agc agt tgc cct gtg ggg acc ttt acc agg cat	706
	Ser Leu Arg Val Cys Ser Ser Cys Pro Val Gly Thr Phe Thr Arg His	
	85 90 95	
10	gag aat ggc ata gag aaa tgc cat gac tgt agt cag cca tgc cca tgg	754
	Glu Asn Gly Ile Glu Lys Cys His Asp Cys Ser Gln Pro Cys Pro Trp	
	100 105 110 115	
15	cca atg att gag aaa tta cct tgt gct gcc ttg act gac cga gaa tgc	802
	Pro Met Ile Glu Lys Leu Pro Cys Ala Ala Leu Thr Asp Arg Glu Cys	
	120 125 130	
20	act tgc cca cct ggc atg ttc cag tct aac gct acc tgt gcc ccc cat	850
	Thr Cys Pro Pro Gly Met Phe Gln Ser Asn Ala Thr Cys Ala Pro His	
	135 140 145	
25	acg gtg tgt cct gtg ggt tgg ggt gtg cgg aag aaa ggg aca gag act	898
	Thr Val Cys Pro Val Gly Trp Gly Val Arg Lys Lys Gly Thr Glu Thr	
	150 155 160	
30	gag gat gtg cgg tgt aag cag tgt gct cgg ggt acc ttc tca gat gtg	946
	Glu Asp Val Arg Cys Lys Gln Cys Ala Arg Gly Thr Phe Ser Asp Val	
	165 170 175	
35	cct tct agt gtg atg aaa tgc aaa gca tac aca gac tgt ctg agt cag	994
	Pro Ser Ser Val Met Lys Cys Lys Ala Tyr Thr Asp Cys Leu Ser Gln	
	180 185 190 195	
40	aac ctg gtg gtg atc aag ccg ggg acc aag gag aca gac aac gtc tgt	1042
	Asn Leu Val Val Ile Lys Pro Gly Thr Lys Glu Thr Asp Asn Val Cys	
	200 205 210	
45	ggc aca ctc ccg tcc ttc tcc agc tcc acc tca cct tcc cct ggc aca	1090
	Gly Thr Leu Pro Ser Phe Ser Ser Ser Thr Ser Pro Ser Pro Gly Thr	
	215 220 225	
50	gcc atc ttt cca cgc cct gag cac atg gaa acc cat gaa gtc cct tcc	1138
	Ala Ile Phe Pro Arg Pro Glu His Met Glu Thr His Glu Val Pro Ser	
	230 235 240	
55	tcc act tat gtt ccc aaa ggc atg aac tca aca gaa tcc aac tct tct	1186
	Ser Thr Tyr Val Pro Lys Gly Met Asn Ser Thr Glu Ser Asn Ser Ser	
	245 250 255	
60	gcc tct gtt aga cca aag gta ctg agt agc atc cag gaa ggg aca gtc	1234
	Ala Ser Val Arg Pro Lys Val Leu Ser Ser Ile Gln Glu Gly Thr Val	
	260 265 270 275	
65	cct gac aac aca agc tca gca agg ggg aag gaa gac gtg aac aag acc	1282
	Pro Asp Asn Thr Ser Ser Ala Arg Gly Lys Glu Asp Val Asn Lys Thr	
	280 285 290	
70	ctc cca aac ctt cag gta gtc aac cac cag caa ggc ccc cac cac aga	1330
	Leu Pro Asn Leu Gln Val Val Asn His Gln Gln Gly Pro His His Arg	
	295 300 305	
75	cac atc ctg aag ctg ctg ccg tcc atg gag gcc act ggg ggc gag aag	1378
	His Ile Leu Lys Leu Leu Pro Ser Met Glu Ala Thr Gly Gly Glu Lys	
	310 315 320	

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5	tcc agc acg ccg atc aag ggc ccc aag agg gga cat cct aga cag aac	1426
	Ser Ser Thr Pro Ile Lys Gly Pro Lys Arg Gly His Pro Arg Gln Asn	
	325 330 335	
10	cta cac aag cat ttt gac atc aat gag cat ttg ccc tgg atg att gtg	1474
	Leu His Lys His Phe Asp Ile Asn Glu His Leu Pro Trp Met Ile Val	
	340 345 350 355	
15	ctt ttc ctg ctg ctg gtg ctt gtg gtg att gtg gtg tgc agt atc cgg	1522
	Leu Phe Leu Leu Leu Val Leu Val Val Ile Val Val Cys Ser Ile Arg	
	360 365 370	
20	aaa agc tcg agg act ctg aaa aag ggg ccc cgg cag gat ccc agt gcc	1570
	Lys Ser Ser Arg Thr Leu Lys Lys Gly Pro Arg Gln Asp Pro Ser Ala	
	375 380 385	
25	att gtg gaa aag gca ggg ctg aag aaa tcc atg act cca acc cag aac	1618
	Ile Val Glu Lys Ala Gly Leu Lys Lys Ser Met Thr Pro Thr Gln Asn	
	390 395 400	
30	cgg gag aaa tgg atc tac tac tgc aat ggc cat ggt atc gat atc ctg	1666
	Arg Glu Lys Trp Ile Tyr Tyr Cys Asn Gly His Gly Ile Asp Ile Leu	
	405 410 415	
35	aag ctt gta gca gcc caa gtg gga agc cag tgg aaa gat atc tat cag	1714
	Lys Leu Val Ala Ala Gln Val Gly Ser Gln Trp Lys Asp Ile Tyr Gln	
	420 425 430 435	
40	ttt ctt tgc aat gcc agt gag agg gag gtt gct gct ttc tcc aat ggg	1762
	Phe Leu Cys Asn Ala Ser Glu Arg Glu Val Ala Ala Phe Ser Asn Gly	
	440 445 450	
45	tac aca gcc gac cac gag cgg gcc tac gca gct ctg cag cac tgg acc	1810
	Tyr Thr Ala Asp His Glu Arg Ala Tyr Ala Ala Leu Gln His Trp Thr	
	455 460 465	
50	atc cgg ggc ccc gag gcc agc ctc gcc cag cta att agc gcc ctg cgc	1858
	Ile Arg Gly Pro Glu Ala Ser Leu Ala Gln Leu Ile Ser Ala Leu Arg	
	470 475 480	
55	cag cac cgg aga aac gat gtt gtg gag aag att cgt ggg ctg atg gaa	1906
	Gln His Arg Arg Asn Asp Val Val Glu Lys Ile Arg Gly Leu Met Glu	
	485 490 495	
60	gac acc acc cag ctg gaa act gac aaa cta gct ctc ccg atg agc ccc	1954
	Asp Thr Thr Gln Leu Thr Asp Lys Leu Ala Leu Pro Met Ser Pro	
	500 505 510 515	
65	agc ccg ctt agc ccg agc ccc atc ccc agc ccc aac gcg aaa ctt gag	2002
	Ser Pro Leu Ser Pro Ser Pro Ile Pro Ser Pro Asn Ala Lys Leu Glu	
	520 525 530	
70	aat tcc gct ctc ctg acg gtg gag cct tcc cca cag gac aag aac aag	2050
	Asn Ser Ala Leu Leu Thr Val Glu Pro Ser Pro Gln Asp Lys Asn Lys	
	535 540 545	
75	ggc ttc ttc gtg gat gag tcg gag ccc ctt ctc cgc tgt gac tct aca	2098
	Gly Phe Phe Val Asp Glu Ser Glu Pro Leu Leu Arg Cys Asp Ser Thr	
	550 555 560	

SUBSTITUTE SHEET (rule 26)

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5	Leu	Thr	Cys	Asp	Lys	Cys	Pro	Ala	Gly	Thr	Tyr	Val	Ser	Glu	His	Cys	65	70	75	80
	Thr	Asn	Thr	Ser	Leu	Arg	Val	Cys	Ser	Ser	Cys	Pro	Val	Gly	Thr	Phe	85	90	95	
10	Thr	Arg	His	Glu	Asn	Gly	Ile	Glu	Lys	Cys	His	Asp	Cys	Ser	Gln	Pro	100	105	110	
	Cys	Pro	Trp	Pro	Met	Ile	Glu	Lys	Leu	Pro	Cys	Ala	Ala	Leu	Thr	Asp	115	120	125	
15	Arg	Glu	Cys	Thr	Cys	Pro	Pro	Gly	Met	Phe	Gln	Ser	Asn	Ala	Thr	Cys	130	135	140	
20	Ala	Pro	His	Thr	Val	Cys	Pro	Val	Gly	Trp	Gly	Val	Arg	Lys	Lys	Gly	145	150	155	160
	Thr	Glu	Thr	Glu	Asp	Val	Arg	Cys	Lys	Gln	Cys	Ala	Arg	Gly	Thr	Phe	165	170	175	
25	Ser	Asp	Val	Pro	Ser	Ser	Val	Met	Lys	Cys	Lys	Ala	Tyr	Thr	Asp	Cys	180	185	190	
	Leu	Ser	Gln	Asn	Leu	Val	Val	Ile	Lys	Pro	Gly	Thr	Lys	Glu	Thr	Asp	195	200	205	
30	Asn	Val	Cys	Gly	Thr	Leu	Pro	Ser	Phe	Ser	Ser	Ser	Thr	Ser	Pro	Ser	210	215	220	
35	Pro	Gly	Thr	Ala	Ile	Phe	Pro	Arg	Pro	Glu	His	Met	Glu	Thr	His	Glu	225	230	235	240
	Val	Pro	Ser	Ser	Thr	Tyr	Val	Pro	Lys	Gly	Met	Asn	Ser	Thr	Glu	Ser	245	250	255	
40	Asn	Ser	Ser	Ala	Ser	Val	Arg	Pro	Lys	Val	Leu	Ser	Ser	Ile	Gln	Glu	260	265	270	
	Gly	Thr	Val	Pro	Asp	Asn	Thr	Ser	Ser	Ala	Arg	Gly	Lys	Glu	Asp	Val	275	280	285	
45	Asn	Lys	Thr	Leu	Pro	Asn	Leu	Gln	Val	Val	Asn	His	Gln	Gln	Gly	Pro	290	295	300	
50	His	His	Arg	His	Ile	Leu	Lys	Leu	Leu	Pro	Ser	Met	Glu	Ala	Thr	Gly	305	310	315	320
	Gly	Glu	Lys	Ser	Ser	Thr	Pro	Ile	Lys	Gly	Pro	Lys	Arg	Gly	His	Pro	325	330	335	
55	Arg	Gln	Asn	Leu	His	Lys	His	Phe	Asp	Ile	Asn	Glu	His	Leu	Pro	Trp	340	345	350	
	Met	Ile	Val	Leu	Phe	Leu	Leu	Leu	Val	Leu	Val	Val	Ile	Val	Val	Cys	355	360	365	
60	Ser	Ile	Arg	Lys	Ser	Ser	Arg	Thr	Leu	Lys	Lys	Gly	Pro	Arg	Gln	Asp	370	375	380	

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5	Pro	Ser	Ala	Ile	Val	Glu	Lys	Ala	Gly	Leu	Lys	Lys	Ser	Met	Thr	Pro	385	390	395	400
	Thr	Gln	Asn	Arg	Glu	Lys	Trp	Ile	Tyr	Tyr	Cys	Asn	Gly	His	Gly	Ile	405	410	415	
10	Asp	Ile	Leu	Lys	Leu	Val	Ala	Ala	Gln	Val	Gly	Ser	Gln	Trp	Lys	Asp	420	425	430	
	Ile	Tyr	Gln	Phe	Leu	Cys	Asn	Ala	Ser	Glu	Arg	Glu	Val	Ala	Ala	Phe	435	440	445	
15	Ser	Asn	Gly	Tyr	Thr	Ala	Asp	His	Glu	Arg	Ala	Tyr	Ala	Ala	Leu	Gln	450	455	460	
20	His	Trp	Thr	Ile	Arg	Gly	Pro	Glu	Ala	Ser	Leu	Ala	Gln	Leu	Ile	Ser	465	470	475	480
	Ala	Leu	Arg	Gln	His	Arg	Arg	Asn	Asp	Val	Val	Glu	Lys	Ile	Arg	Gly	485	490	495	
25	Leu	Met	Glu	Asp	Thr	Thr	Gln	Leu	Glu	Thr	Asp	Lys	Leu	Ala	Leu	Pro	500	505	510	
	Met	Ser	Pro	Ser	Pro	Leu	Ser	Pro	Ser	Pro	Ile	Pro	Ser	Pro	Asn	Ala	515	520	525	
30	Lys	Leu	Glu	Asn	Ser	Ala	Leu	Leu	Thr	Val	Glu	Pro	Ser	Pro	Gln	Asp	530	535	540	
35	Lys	Asn	Lys	Gly	Phe	Phe	Val	Asp	Glu	Ser	Glu	Pro	Leu	Leu	Arg	Cys	545	550	555	560
	Asp	Ser	Thr	Ser	Ser	Gly	Ser	Ser	Ala	Leu	Ser	Arg	Asn	Gly	Ser	Phe	565	570	575	
40	Ile	Thr	Lys	Glu	Lys	Lys	Asp	Thr	Val	Leu	Arg	Gln	Val	Arg	Leu	Asp	580	585	590	
	Pro	Cys	Asp	Leu	Gln	Pro	Ile	Phe	Asp	Asp	Met	Leu	His	Phe	Leu	Asn	595	600	605	
45	Pro	Glu	Glu	Leu	Arg	Val	Ile	Glu	Glu	Ile	Pro	Gln	Ala	Glu	Asp	Lys	610	615	620	
50	Leu	Asp	Arg	Leu	Phe	Glu	Ile	Ile	Gly	Val	Lys	Ser	Gln	Glu	Ala	Ser	625	630	635	640
	Gln	Thr	Leu	Leu	Asp	Ser	Val	Tyr	Ser	His	Leu	Pro	Asp	Leu	Leu		645	650	655	
55	<210> 11																			
	<211> 1474																			
	<212> DNA																			
	<213> Unknown																			
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SUBSTITUTE SHEET (rule 26)

23

<221> CDS
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<400> 11
 atg ggg acc tct ccg agc agc agc acc gcc ctc gcc tcc tgc agc cgc 48
 Met Gly Thr Ser Pro Ser Ser Ser Thr Ala Leu Ala Ser Cys Ser Arg
 10 1 5 10 15

atc gcc cgc cga gcc aca gcc acg atg atc gcg ggc tcc ctt ctc ctg 96
 Ile Ala Arg Arg Ala Thr Ala Thr Met Ile Ala Gly Ser Leu Leu Leu
 20 25 30

15 ctt gga ttc ctt agc acc acc aca gct cag cca gaa cag aag gcc tcg 144
 Leu Gly Phe Leu Ser Thr Thr Thr Ala Gln Pro Glu Gln Lys Ala Ser
 35 40 45

20 aat ctc att ggc aca tac cgc cat gtt gac cgt gcc acc ggc cag gtg 192
 Asn Leu Ile Gly Thr Tyr Arg His Val Asp Arg Ala Thr Gly Gln Val
 50 55 60

25 cta acc tgt gac aag tgt cca gca gga acc tat gtc tct gag cat tgt 240
 Leu Thr Cys Asp Lys Cys Pro Ala Gly Thr Tyr Val Ser Glu His Cys
 65 70 75 80

30 acc aac aca agc ctg cgc gtc tgc agc agt tgc cct gtg ggg acc ttt 288
 Thr Asn Thr Ser Leu Arg Val Cys Ser Ser Cys Pro Val Gly Thr Phe
 85 90 95

35 acc agg cat gag aat ggc ata gag aaa tgc cat gac tgt agt cag cca 336
 Thr Arg His Glu Asn Gly Ile Glu Lys Cys His Asp Cys Ser Gln Pro
 100 105 110

tgc cca tgg cca atg att gag aaa tta cct tgt gct gcc ttg act gac 384
 Cys Pro Trp Pro Met Ile Glu Lys Leu Pro Cys Ala Ala Leu Thr Asp
 115 120 125

40 cga gaa tgc act tgc cca cct ggc atg ttc cag tct aac gct acc tgt 432
 Arg Glu Cys Thr Cys Pro Pro Gly Met Phe Gln Ser Asn Ala Thr Cys
 130 135 140

45 gcc ccc cat acg gtg tgt cct gtg ggt tgg ggt gtg cgg aag aaa ggg 480
 Ala Pro His Thr Val Cys Pro Val Gly Trp Gly Val Arg Lys Lys Gly
 145 150 155 160

50 aca gag act gag gat gtg cgg tgt aag cag tgt gct cgg ggt acc ttc 528
 Thr Glu Thr Glu Asp Val Arg Cys Lys Gln Cys Ala Arg Gly Thr Phe
 165 170 175

tca gat gtg cct tct agt gtg atg aaa tgc aaa gca tac aca gac tgt 576
 Ser Asp Val Pro Ser Ser Val Met Lys Cys Lys Ala Tyr Thr Asp Cys
 180 185 190

55 ctg agt cag aac ctg gtg gtg atc aag ccg ggg acc aag gag aca gac 624
 Leu Ser Gln Asn Leu Val Val Ile Lys Pro Gly Thr Lys Glu Thr Asp
 195 200 205

60 aac gtc tgt ggc aca ctc ccg tcc ttc tcc agc tcc acc tca cct tcc 672
 Asn Val Cys Gly Thr Leu Pro Ser Phe Ser Ser Ser Thr Ser Pro Ser
 210 215 220

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24

5	cct ggc aca gcc atc ttt cca cgc cct gag cac atg gaa acc cat gaa Pro Gly Thr Ala Ile Phe Pro Arg Pro Glu His Met Glu Thr His Glu 225 230 235 240	720
10	gtc cct tcc tcc act tat gtt ccc aaa ggc atg aac tca aca gaa tcc Val Pro Ser Ser Thr Tyr Val Pro Lys Gly Met Asn Ser Thr Glu Ser 245 250 255	768
15	aac tct tct gcc tct gtt aga cca aag gta ctg agt agc atc cag gaa Asn Ser Ser Ala Ser Val Arg Pro Lys Val Leu Ser Ser Ile Gln Glu 260 265 270	816
20	ggg aca gtc cct gac aac aca agc tca gca agg ggg aag gaa gac gtg Gly Thr Val Pro Asp Asn Thr Ser Ala Arg Gly Lys Glu Asp Val 275 280 285	864
25	aac aag acc ctc cca aac ctt cag gta gtc aac cac cag caa ggc ccc Asn Lys Thr Leu Pro Asn Leu Gln Val Val Asn His Gln Gln Gly Pro 290 295 300	912
30	cac cac aga cac atc ctg aag ctg ctg ccg tcc atg gag gcc act ggg His His Arg His Ile Leu Lys Leu Leu Pro Ser Met Glu Ala Thr Gly 305 310 315 320	960
35	ggc gag aag tcc agc acg ccc atc aag ggc ccc aag agg gga cat cct Gly Glu Lys Ser Ser Thr Pro Ile Lys Gly Pro Lys Arg Gly His Pro 325 330 335	1008
40	aga cag aac cta cac aag cat ttt gac atc aat gag cat ttg ccc tgg Arg Gln Asn Leu His Lys His Phe Asp Ile Asn Glu His Leu Pro Trp 340 345 350	1056
45	atg att gtg ctt ttc ctg ctg ctg gtg ctt gtg gtg att gtg gtg tgc Met Ile Val Leu Phe Leu Leu Val Leu Val Val Ile Val Val Cys 355 360 365	1104
50	agt atc cgg aaa agc tcg agg act ctg aaa aag ggg ccc cgg cag gat Ser Ile Arg Lys Ser Ser Arg Thr Leu Lys Lys Gly Pro Arg Gln Asp 370 375 380	1152
55	ccc agt gcc att gtg gaa aag gca ggg ctg aag aaa tcc atg act cca Pro Ser Ala Ile Val Glu Lys Ala Gly Leu Lys Lys Ser Met Thr Pro 385 390 395 400	1200
60	acc cag aac cgg gag aaa tgg atc tac tac tgc aat ggc cat gga ccc Thr Gln Asn Arg Glu Lys Trp Ile Tyr Tyr Cys Asn Gly His Gly Pro 405 410 415	1248
65	cat gat gag gag tgg ggg ttg atg gag aga cat att caa gat att tat His Asp Glu Glu Trp Gly Leu Met Glu Arg His Ile Gln Asp Ile Tyr 420 425 430	1296
70	att caa aga agc aat caa gat tca gaa aga tgg ggt tgataatttt Ile Gln Arg Ser Asn Gln Asp Ser Glu Arg Trp Gly 435 440	1342
75	tacttcaccc tgggaggcag catagtgcag tgaaaggat cgatatacctg aagcttgtag cagcccaagt gggaagccag tggaaagata tctatcagtt tctttgcaat gccagtgaga gggaggttgc tg	1402 1462 1474

SUBSTITUTE SHEET (rule 26)

25

5
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 <211> 444
 <212> PRT
 <213> Unknown

10
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 1 5 10 15

15
 Ile Ala Arg Arg Ala Thr Ala Thr Met Ile Ala Gly Ser Leu Leu Leu
 20 25 30
 Leu Gly Phe Leu Ser Thr Thr Thr Ala Gln Pro Glu Gln Lys Ala Ser
 35 40 45

20
 Asn Leu Ile Gly Thr Tyr Arg His Val Asp Arg Ala Thr Gly Gln Val
 50 55 60

25
 Leu Thr Cys Asp Lys Cys Pro Ala Gly Thr Tyr Val Ser Glu His Cys
 65 70 75 80
 Thr Asn Thr Ser Leu Arg Val Cys Ser Ser Cys Pro Val Gly Thr Phe
 85 90 95

30
 Thr Arg His Glu Asn Gly Ile Glu Lys Cys His Asp Cys Ser Gln Pro
 100 105 110
 Cys Pro Trp Pro Met Ile Glu Lys Leu Pro Cys Ala Ala Leu Thr Asp
 115 120 125

35
 Arg Glu Cys Thr Cys Pro Pro Gly Met Phe Gln Ser Asn Ala Thr Cys
 130 135 140

40
 Ala Pro His Thr Val Cys Pro Val Gly Trp Gly Val Arg Lys Lys Gly
 145 150 155 160
 Thr Glu Thr Glu Asp Val Arg Cys Lys Gln Cys Ala Arg Gly Thr Phe
 165 170 175

45
 Ser Asp Val Pro Ser Ser Val Met Lys Cys Lys Ala Tyr Thr Asp Cys
 180 185 190
 Leu Ser Gln Asn Leu Val Val Ile Lys Pro Gly Thr Lys Glu Thr Asp
 195 200 205

50
 Asn Val Cys Gly Thr Leu Pro Ser Phe Ser Ser Ser Thr Ser Pro Ser
 210 215 220

55
 Pro Gly Thr Ala Ile Phe Pro Arg Pro Glu His Met Glu Thr His Glu
 225 230 235 240
 Val Pro Ser Ser Thr Tyr Val Pro Lys Gly Met Asn Ser Thr Glu Ser
 245 250 255

60
 Asn Ser Ser Ala Ser Val Arg Pro Lys Val Leu Ser Ser Ile Gln Glu
 260 265 270
 Gly Thr Val Pro Asp Asn Thr Ser Ser Ala Arg Gly Lys Glu Asp Val
 275 280 285

SUBSTITUTE SHEET (rule 26)

5 Asn Lys Thr Leu Pro Asn Leu Gln Val Val Asn His Gln Gln Gly Pro
 290 295 300
 His His Arg His Ile Leu Lys Leu Leu Pro Ser Met Glu Ala Thr Gly
 305 310 315 320
 10 Gly Glu Lys Ser Ser Thr Pro Ile Lys Gly Pro Lys Arg Gly His Pro
 325 330 335
 15 Arg Gln Asn Leu His Lys His Phe Asp Ile Asn Glu His Leu Pro Trp
 340 345 350
 Met Ile Val Leu Phe Leu Leu Leu Val Leu Val Val Ile Val Val Cys
 355 360 365
 20 Ser Ile Arg Lys Ser Ser Arg Thr Leu Lys Lys Gly Pro Arg Gln Asp
 370 375 380
 Pro Ser Ala Ile Val Glu Lys Ala Gly Leu Lys Lys Ser Met Thr Pro
 385 390 395 400
 25 Thr Gln Asn Arg Glu Lys Trp Ile Tyr Tyr Cys Asn Gly His Gly Pro
 405 410 415
 30 His Asp Glu Glu Trp Gly Leu Met Glu Arg His Ile Gln Asp Ile Tyr
 420 425 430
 Ile Gln Arg Ser Asn Gln Asp Ser Glu Arg Trp Gly
 435 440
 35 <210> 13
 <211> 227
 <212> PRT
 <213> Unknown
 40 <220>
 <223> Description of Unknown Organism:rodent
 <400> 13
 45 Met Ala Pro Ala Ala Leu Trp Val Ala Leu Val Phe Glu Leu Gln Leu
 1 5 10 15
 Trp Ala Thr Gly His Thr Val Pro Ala Gln Val Val Leu Thr Pro Tyr
 20 25 30
 50 Lys Pro Glu Pro Gly Tyr Glu Cys Gln Ile Ser Gln Glu Tyr Tyr Asp
 35 40 45
 55 Arg Lys Ala Gln Met Cys Cys Ala Lys Cys Pro Pro Gly Gln Tyr Val
 50 55 60
 Lys His Phe Cys Asn Lys Thr Ser Asp Thr Val Cys Ala Asp Cys Glu
 65 70 75 80
 60 Ala Ser Met Tyr Thr Gln Val Trp Asn Gln Phe Arg Thr Cys Leu Ser
 85 90 95
 Cys Ser Ser Ser Cys Thr Thr Asp Gln Val Glu Ile Arg Ala Cys Thr
 100 105 110

SUBSTITUTE SHEET (rule 26)

5 Lys Gln Gln Asn Arg Val Cys Ala Cys Glu Ala Gly Arg Tyr Cys Ala
 115 120 125
 Leu Lys Thr His Ser Gly Ser Cys Arg Gln Cys Met Arg Leu Ser Lys
 130 135 140
 10 Cys Gly Pro Gly Phe Gly Val Ala Ser Ser Arg Ala Pro Asn Gly Asn
 145 150 155 160
 Val Leu Cys Lys Ala Cys Ala Pro Gly Thr Phe Ser Asp Thr Thr Ser
 165 170 175
 Ser Thr Asp Val Cys Arg Pro His Arg Ile Cys Ser Ile Leu Ala Ile
 180 185 190
 20 Pro Gly Asn Ala Ser Thr Asp Ala Val Cys Ala Pro Glu Ser Pro Thr
 195 200 205
 Leu Ser Ala Ile Pro Arg Thr Leu Tyr Val Ser Gln Pro Glu Pro Thr
 210 215 220
 25 Arg Ser Gln
 225
 30 <210> 14
 <211> 225
 <212> PRT
 <213> Unknown
 35 <220>
 <223> Description of Unknown Organism:primate
 <400> 14
 40 Met Ala Pro Val Ala Val Trp Ala Ala Leu Ala Val Gly Leu Glu Leu
 1 5 10 15
 Trp Ala Ala Ala His Ala Leu Pro Ala Gln Val Ala Phe Thr Pro Tyr
 20 25 30
 45 Ala Pro Glu Pro Gly Ser Thr Cys Arg Leu Arg Glu Tyr Tyr Asp Gln
 35 40 45
 Thr Ala Gln Met Cys Cys Ser Lys Cys Ser Pro Gly Gln His Ala Lys
 50 55 60
 50 Val Phe Cys Thr Lys Thr Ser Asp Thr Val Cys Asp Ser Cys Glu Asp
 65 70 75 80
 Ser Thr Tyr Thr Gln Leu Trp Asn Trp Val Pro Glu Cys Leu Ser Cys
 85 90 95
 55 Gly Ser Arg Cys Ser Ser Asp Gln Val Glu Thr Gln Ala Cys Thr Arg
 100 105 110
 60 Glu Gln Asn Arg Ile Cys Thr Cys Arg Pro Gly Trp Tyr Cys Ala Leu
 115 120 125
 Ser Lys Gln Glu Gly Cys Arg Leu Cys Ala Pro Leu Arg Lys Cys Arg
 130 135 140

SUBSTITUTE SHEET (rule 26)

5 Pro Gly Phe Gly Val Ala Arg Pro Gly Thr Glu Thr Ser Asp Val Val
 145 150 155 160
 Cys Lys Pro Cys Ala Pro Gly Thr Phe Ser Asn Thr Thr Ser Ser Thr
 165 170 175
 10 Asp Ile Cys Arg Pro His Gln Ile Cys Asn Val Val Ala Ile Pro Gly
 180 185 190
 Asn Ala Ser Met Asp Ala Val Cys Thr Ser Thr Ser Pro Thr Arg Ser
 195 200 205
 15 Met Ala Pro Gly Ala Val His Leu Pro Gln Pro Val Ser Thr Arg Ser
 210 215 220
 20 Gln
 225
 <210> 15
 25 <211> 187
 <212> PRT
 <213> Unknown
 <220>
 30 <223> Description of Unknown Organism:primate
 <400> 15
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 1 5 10 15
 35 Lys Trp Thr Thr Gln Glu Thr Phe Pro Pro Lys Tyr Leu His Tyr Asp
 20 25 30
 40 Glu Glu Thr Ser His Gln Leu Leu Cys Asp Lys Cys Pro Pro Gly Thr
 35 40 45
 Tyr Leu Lys Gln His Cys Thr Ala Lys Trp Lys Thr Val Cys Ala Pro
 50 55 60
 45 Cys Pro Asp His Tyr Tyr Thr Asp Ser Trp His Thr Ser Asp Glu Cys
 65 70 75 80
 Leu Tyr Cys Ser Pro Val Cys Lys Glu Leu Gln Tyr Val Lys Gln Glu
 85 90 95
 50 Cys Asn Arg Thr His Asn Arg Val Cys Glu Cys Lys Glu Gly Arg Tyr
 100 105 110
 Leu Glu Ile Glu Phe Cys Leu Lys His Arg Ser Cys Pro Pro Gly Phe
 115 120 125
 55 Gly Val Val Gln Ala Gly Thr Pro Glu Arg Asn Thr Val Cys Lys Arg
 130 135 140
 60 Cys Pro Asp Gly Phe Phe Ser Asn Glu Thr Ser Ser Lys Ala Pro Cys
 145 150 155 160
 Arg Lys His Thr Asn Cys Ser Val Phe Gly Leu Leu Leu Thr Gln Lys
 165 170 175

SUBSTITUTE SHEET (rule 26)

5 Gly Asn Ala Thr His Asp Asn Ile Cys Ser Gly
180 185

10 <210> 16
<211> 636
<212> DNA
<213> Unknown

15 <220>
<223> Description of Unknown Organism:rodent
<220>
<221> CDS
<222> (104)..(553)

20 <400> 16
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25 cagcactggc gagtagcagg aataaacacg tttggtgaga gcc atg gca ctc aag 115
Met Ala Leu Lys
1

30 gtc cta cct cta cac agg acg gtg ctc ttc gct gcc att ctc ttc cta 163
Val Leu Pro Leu His Arg Thr Val Leu Phe Ala Ala Ile Leu Phe Leu
5 10 15 20

35 ctc cac ctg gca tgt aaa gtg agt tgc gaa acc gga gat tgc agg cag 211
Leu His Leu Ala Cys Lys Val Ser Cys Glu Thr Gly Asp Cys Arg Gln
25 30 35

40 cag gaa ttc aag gat cga tct gga aac tgt gtc ctc tgc aaa cag tgc 259
Gln Glu Phe Lys Asp Arg Ser Gly Asn Cys Val Leu Cys Lys Gln Cys
40 45 50

45 gga cct ggc atg gag ttg tcc aag gaa tgt ggc ttc ggc tat ggg gag 307
Gly Pro Gly Met Glu Leu Ser Lys Glu Cys Gly Phe Gly Tyr Gly Glu
55 60 65

50 gat gca cag tgt gtg ccc tgc agg ccg cac cgg ttc aag gaa gac tgg 355
Asp Ala Gln Cys Val Pro Cys Arg Pro His Arg Phe Lys Glu Asp Trp
70 75 80

55 ggt ttc cag aag tgt aag cca tgt gcg gac tgt gcg ctg gtg aac cgc 403
Gly Phe Gln Lys Cys Lys Pro Cys Ala Asp Cys Ala Leu Val Asn Arg
85 90 95 100

60 ttt cag agg gcc aac tgc tca cac acc agt gat gct gtc tgc ggg gac 451
Phe Gln Arg Ala Asn Cys Ser His Thr Ser Asp Ala Val Cys Gly Asp
105 110 115

65 tgc ctg cca gga ttt tac cgg aag acc aaa ctg gtt ggt ttt caa gac 499
Cys Leu Pro Gly Phe Tyr Arg Lys Thr Lys Leu Val Gly Phe Gln Asp
120 125 130

70 atg gag tgt gtg ccc tgc gga gac cca cct cct ccc tac gaa cca cac 547
Met Glu Cys Val Pro Cys Gly Asp Pro Pro Pro Pro Tyr Glu Pro His
135 140 145

SUBSTITUTE SHEET (rule 26)

30

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5      tgt gag tgaatgtgccca agtgggcagca gaccttttaa aaaaaaagaa aaaaaaaciaa 603
      Cys Glu
      150

      acaaaaaaciaa aaaaaaaaaa aaaaaaaaaa aaa 636

10     <210> 17
      <211> 150
      <212> PRT
      <213> Unknown

15     <400> 17
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      1 5 10 15

20     Ile Leu Phe Leu Leu His Leu Ala Cys Lys Val Ser Cys Glu Thr Gly
      20 25 30

      Asp Cys Arg Gln Gln Glu Phe Lys Asp Arg Ser Gly Asn Cys Val Leu
      35 40 45

25     Cys Lys Gln Cys Gly Pro Gly Met Glu Leu Ser Lys Glu Cys Gly Phe
      50 55 60

30     Gly Tyr Gly Glu Asp Ala Gln Cys Val Pro Cys Arg Pro His Arg Phe
      65 70 75 80

      Lys Glu Asp Trp Gly Phe Gln Lys Cys Lys Pro Cys Ala Asp Cys Ala
      85 90 95

35     Leu Val Asn Arg Phe Gln Arg Ala Asn Cys Ser His Thr Ser Asp Ala
      100 105 110

      Val Cys Gly Asp Cys Leu Pro Gly Phe Tyr Arg Lys Thr Lys Leu Val
      115 120 125

40     Gly Phe Gln Asp Met Glu Cys Val Pro Cys Gly Asp Pro Pro Pro Pro
      130 135 140

45     Tyr Glu Pro His Cys Glu
      145 150

      <210> 18
      <211> 474
      <212> DNA
      <213> Unknown

      <220>
      <223> Description of Unknown Organism:primate

55     <220>
      <221> CDS
      <222> (78) .. (473)

60     <400> 18

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ttaccggcct tcccacc atg gat tgc caa gaa aat gag tac tgg gac caa 110

SUBSTITUTE SHEET (rule 26)

31

	Met Asp Cys Gln Glu Asn Glu Tyr Trp Asp Gln																			
	1					5					10									
5	tgg	gga	cgg	tgt	gtc	acc	tgc	caa	cgg	tgt	ggt	cct	gga	cag	gag	cta			158	
	Trp	Gly	Arg	Cys	Val	Thr	Cys	Gln	Arg	Cys	Gly	Pro	Gly	Gln	Glu	Leu				
	15					20					25									
10	tcc	aag	gat	tgt	ggt	tat	gga	gag	ggt	gga	gat	gcc	tac	tgc	aca	gcc			206	
	Ser	Lys	Asp	Cys	Gly	Tyr	Gly	Glu	Gly	Gly	Asp	Ala	Tyr	Cys	Thr	Ala				
	30					35					40									
15	tgc	cct	cct	cgc	agt	aca	aaa	gca	gct	ggg	gcc	acc	aca	aat	gtc	aga			254	
	Cys	Pro	Pro	Arg	Ser	Thr	Lys	Ala	Ala	Gly	Ala	Thr	Thr	Asn	Val	Arg				
	45					50					55									
20	gtt	gca	tca	cct	gtg	ctg	tca	tca	atc	gtg	ttc	aga	agg	ttc	aac	tgc			302	
	Val	Ala	Ser	Pro	Val	Leu	Ser	Ser	Ile	Val	Phe	Arg	Arg	Phe	Asn	Cys				
	60					65					70					75				
25	aca	gtt	acc	tct	nat	gct	gtc	tgt	ggg	gga	ngg	ttt	gcc	caa	gtt	tct			350	
	Thr	Xaa	Thr	Ser	Xaa	Ala	Val	Cys	Gly	Gly	Xaa	Phe	Ala	Gln	Val	Ser				
	80					85					90									
30	aac	cga	aag	aca	cgc	cat	tgg	aag	gct	gcc	agg	acc	aag	gat	ggc	atc			398	
	Asn	Arg	Lys	Thr	Arg	His	Trp	Lys	Ala	Ala	Arg	Thr	Lys	Asp	Gly	Ile				
	95					100					105									
35	ccg	tgg	cac	aaa	gnc	aga	ccc	cca	act	tct	gan	ggt	tnc	aaa	gtg	nct			446	
	Pro	Trp	His	Lys	Xaa	Arg	Pro	Pro	Thr	Ser	Xaa	Gly	Xaa	Lys	Val	Xaa				
	110					115					120									
40	ttc	caa	ttg	gag	ctt	aat	ggg	agg	can	a									474	
	Phe	Gln	Leu	Glu	Leu	Asn	Gly	Arg	Xaa											
	125					130														
45	<210> 19																			
	<211> 132																			
	<212> PRT																			
	<213> Unknown																			
50	<400> 19																			
	Met	Asp	Cys	Gln	Glu	Asn	Glu	Tyr	Trp	Asp	Gln	Trp	Gly	Arg	Cys	Val				
	1				5					10					15					
	Thr	Cys	Gln	Arg	Cys	Gly	Pro	Gly	Gln	Glu	Leu	Ser	Lys	Asp	Cys	Gly				
	20					25					30									
	Tyr	Gly	Glu	Gly	Gly	Asp	Ala	Tyr	Cys	Thr	Ala	Cys	Pro	Pro	Arg	Ser				
	35					40					45									
55	Thr	Lys	Ala	Ala	Gly	Ala	Thr	Thr	Asn	Val	Arg	Val	Ala	Ser	Pro	Val				
	50					55					60									
	Leu	Ser	Ser	Ile	Val	Phe	Arg	Arg	Phe	Asn	Cys	Thr	Xaa	Thr	Ser	Xaa				
	65					70					75					80				
60	Ala	Val	Cys	Gly	Gly	Xaa	Phe	Ala	Gln	Val	Ser	Asn	Arg	Lys	Thr	Arg				
	85					90					95									

SUBSTITUTE SHEET (rule 26)

32

5 His Trp Lys Ala Ala Arg Thr Lys Asp Gly Ile Pro Trp His Lys Xaa
 100 105 110
 Arg Pro Pro Thr Ser Xaa Gly Xaa Lys Val Xaa Phe Gln Leu Glu Leu
 115 120 125
 10 Asn Gly Arg Xaa
 130
 15 <210> 20
 <211> 546
 <212> DNA
 <213> Unknown
 20 <220>
 <223> Description of Unknown Organism:primate
 <220>
 <221> CDS
 <222> (78)..(308)
 25 <400> 20
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 ttaccggcct tcccacc atg gat tgc caa gaa aat gag tac tgg gac caa 110
 Met Asp Cys Gln Glu Asn Glu Tyr Trp Asp Gln
 1 5 10
 tgg gga cgg tgt gtc acc tgc caa cgg tgt ggt cct gga cag gag cta 158
 Trp Gly Arg Cys Val Thr Cys Gln Arg Cys Gly Pro Gly Gln Glu Leu
 15 20 25
 tcc aag gat tgt ggt tat gga gag ggt gga gat gcc tac tgc aca gcc 206
 Ser Lys Asp Cys Gly Tyr Gly Glu Gly Gly Asp Ala Tyr Cys Thr Ala
 30 35 40
 40 tgc cct cct cgc agg tac aaa agc agc tgg ggc cac cac aaa tgt cag 254
 Cys Pro Pro Arg Arg Tyr Lys Ser Ser Trp Gly His His Lys Cys Gln
 45 50 55
 45 agt tgc atc acc tgt gct gtc atc aat cgt gtt cag aag gtc caa ctg 302
 Ser Cys Ile Thr Cys Ala Val Ile Asn Arg Val Gln Lys Val Gln Leu
 60 65 70 75
 50 cac agc taacctctna tgctgtctgt ggggatgttt gncccaagtt ctnaccgaaa 358
 His Ser
 agacacgcca tgggaaggct ggcaggacca ngaatggccn tcccgtggca gaaagccaga 418
 ccccccaacn nctgnagggt ccaatgtggc cttncattt ggaagcttan tgggaaggca 478
 55 gatgncaacc caaagtggcc ccttcaggga ggccaaaatt tggttggaat ggggtgnagca 538
 gcntgcca 546

SUBSTITUTE SHEET (rule 26)

33

5 <210> 21
 <211> 77
 <212> PRT
 <213> Unknown
 <400> 21

10 Met Asp Cys Gln Glu Asn Glu Tyr Trp Asp Gln Trp Gly Arg Cys Val
 1 5 10 15

15 Thr Cys Gln Arg Cys Gly Pro Gly Gln Glu Leu Ser Lys Asp Cys Gly
 20 25 30

Tyr Gly Glu Gly Gly Asp Ala Tyr Cys Thr Ala Cys Pro Pro Arg Arg
 35 40 45

20 Tyr Lys Ser Ser Trp Gly His His Lys Cys Gln Ser Cys Ile Thr Cys
 50 55 60

Ala Val Ile Asn Arg Val Gln Lys Val Gln Leu His Ser
 65 70 75

25 <210> 22
 <211> 932
 <212> DNA
 30 <213> Unknown

<220>
 <223> Description of Unknown Organism:primate

35 <220>
 <221> CDS
 <222> (78)..(770)

40 <220>
 <221> misc_feature
 <222> (782)
 <223> nucleotide may be A, C, G, or T

<400> 22

45 cgcgctgagg tggatttgta ccggagtcac atttggggagc aagagccatc tactcggtccg 60
 ttaccggcct tcccacc atg gat tgc caa gaa aat gag tac tgg gac caa 110
 Met Asp Cys Gln Glu Asn Glu Tyr Trp Asp Gln
 1 5 10

50 tgg gga cgg tgt gtc acc tgc caa cgg tgt ggt cct gga cag gag cta 158
 Trp Gly Arg Cys Val Thr Cys Gln Arg Cys Gly Pro Gly Gln Glu Leu
 15 20 25

55 tcc aag gat tgt ggt tat gga gag ggt gga gat gcc tac tgc aca gcc 206
 Ser Lys Asp Cys Gly Tyr Gly Glu Gly Gly Asp Ala Tyr Cys Thr Ala
 30 35 40

60 tgc cct cct cgc agg tac aaa agc agc tgg ggc cac cac aaa tgt cag 254
 Cys Pro Pro Arg Arg Tyr Lys Ser Ser Trp Gly His His Lys Cys Gln
 45 50 55

SUBSTITUTE SHEET (rule 26)

34

5	agt tgc atc acc tgt gct gtc atc aat cgt gtt cag aag gtc aac tgc Ser Cys Ile Thr Cys Ala Val Ile Asn Arg Val Gln Lys Val Asn Cys 60 65 70 75	302
10	aca gct acc tct aat gct gtc tgt ggg gac tgt ttg ccc agg ttc tac Thr Ala Thr Ser Asn Ala Val Cys Gly Asp Cys Leu Pro Arg Phe Tyr 80 85 90	350
15	cga aag aca cgc att gga ggc ctg cag gac caa gag tgc atc ccg tgc Arg Lys Thr Arg Ile Gly Gly Leu Gln Asp Gln Glu Cys Ile Pro Cys 95 100 105	398
20	acg aag cag acc ccc acc tct gag gtt caa tgt gcc ttc cag ttg agc Thr Lys Gln Thr Pro Thr Ser Glu Val Gln Cys Ala Phe Gln Leu Ser 110 115 120	446
25	tta gtg gag gca gat gca ccc aca gtg ccc cct cag gag gcc aca ctt Leu Val Glu Ala Asp Ala Pro Thr Val Pro Pro Gln Glu Ala Thr Leu 125 130 135	494
30	gtt gca ctg gtg agc agc ctg cta gtg gtg ttt acc ctg gcc ttc ctg Val Ala Leu Val Ser Ser Leu Leu Val Val Phe Thr Leu Ala Phe Leu 140 145 150 155	542
35	ggg ctc ttc ttc ctc tac tgc aag cag ttc ttc aac aga cat tgc cag Gly Leu Phe Phe Leu Tyr Cys Lys Gln Phe Phe Asn Arg His Cys Gln 160 165 170	590
40	cgt gga ggt ttg ctg cag ttt gag gct gat aaa aca gca aag gag gaa Arg Gly Gly Leu Leu Gln Phe Glu Ala Asp Lys Thr Ala Lys Glu Glu 175 180 185	638
45	tct ctc ttc ccc gtg cca ccc agc aag gag acc agt gct gag tcc caa Ser Leu Phe Pro Val Pro Pro Ser Lys Glu Thr Ser Ala Glu Ser Gln 190 195 200	686
50	gtc tct tgg gcc cct ggc agc ctt gcc cag ttg ttc tct ctg gac tct Val Ser Trp Ala Pro Gly Ser Leu Ala Gln Leu Phe Ser Leu Asp Ser 205 210 215	734
55	gtt cct ata cca caa cag cag cag ggg cct gaa atg tgatgtccac Val Pro Ile Pro Gln Gln Gln Gln Gly Pro Glu Met 220 225 230	780
60	angagctaata accctacaga tggggcatat cctatcccat cccaccagag gattgattct ccatttcaca aggactgac tggagcattt cttgcttccc tggtgtagtc tggggagcca gattccacat tcatgggact accagacatg tt	840 900 932
55	<210> 23 <211> 231 <212> PRT <213> Unknown	
60	<400> 23	

Met Asp Cys Gln Glu Asn Glu Tyr Trp Asp Gln Trp Gly Arg Cys Val
1 5 10 15

SUBSTITUTE SHEET (rule 26)

35

5 Thr Cys Gln Arg Cys Gly Pro Gly Gln Glu Leu Ser Lys Asp Cys Gly
 20 25 30
 Tyr Gly Glu Gly Gly Asp Ala Tyr Cys Thr Ala Cys Pro Pro Arg Arg
 35 40 45
 10 Tyr Lys Ser Ser Trp Gly His His Lys Cys Gln Ser Cys Ile Thr Cys
 50 55 60
 15 Ala Val Ile Asn Arg Val Gln Lys Val Asn Cys Thr Ala Thr Ser Asn
 65 70 75 80
 Ala Val Cys Gly Asp Cys Leu Pro Arg Phe Tyr Arg Lys Thr Arg Ile
 85 90 95
 20 Gly Gly Leu Gln Asp Gln Glu Cys Ile Pro Cys Thr Lys Gln Thr Pro
 100 105 110
 Thr Ser Glu Val Gln Cys Ala Phe Gln Leu Ser Leu Val Glu Ala Asp
 115 120 125
 25 Ala Pro Thr Val Pro Pro Gln Glu Ala Thr Leu Val Ala Leu Val Ser
 130 135 140
 30 Ser Leu Leu Val Val Phe Thr Leu Ala Phe Leu Gly Leu Phe Phe Leu
 145 150 155 160
 Tyr Cys Lys Gln Phe Phe Asn Arg His Cys Gln Arg Gly Gly Leu Leu
 165 170 175
 35 Gln Phe Glu Ala Asp Lys Thr Ala Lys Glu Glu Ser Leu Phe Pro Val
 180 185 190
 Pro Pro Ser Lys Glu Thr Ser Ala Glu Ser Gln Val Ser Trp Ala Pro
 195 200 205
 40 Gly Ser Leu Ala Gln Leu Phe Ser Leu Asp Ser Val Pro Ile Pro Gln
 210 215 220
 45 Gln Gln Gln Gly Pro Glu Met
 225 230

 50 <210> 24
 <211> 232
 <212> DNA
 <213> Unknown

 <220>
 <223> Description of Unknown Organism:primate
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 <400> 24
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 60 ggcagcctgt gcttcaagcc cgtagttgta ttcattccct aaaggggcca ttccgtttgt 180
 atcatcacat gtcctcagtg ggtccatgtg tatatcaagg acatgatgca ga 232

SUBSTITUTE SHEET (rule 26)

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5      <210> 25
      <211> 77
      <212> PRT
      <213> Unknown

      <220>

10     <223> Description of Unknown Organism:primate

      <400> 25
      Leu Ala Leu Gly Thr Lys Leu Leu Ser Ser Ser Val Gly Leu Asn Leu
        1              5              10              15
15     Ser Xaa Lys Cys Cys Phe Ser Tyr Thr Arg Ser Arg Ser Arg Val Ser
        20              25              30
20     Cys Ile Met Ala Ser Tyr Xaa Ser Gly Ser Leu Cys Phe Lys Pro Val
        35              40              45
      Val Val Phe Ile Pro Xaa Arg Gly His Ser Val Cys Ile Ile Thr Cys
        50              55              60
25     Pro Gln Trp Val His Val Tyr Ile Lys Asp Met Met Gln
        65              70              75

30     <210> 26
      <211> 72
      <212> PRT
      <213> Unknown

      <220>

35     <223> Description of Unknown Organism:primate

      <400> 26
      Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro Ser Glu Cys
        1              5              10              15
40     Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp
        20              25              30
45     Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile
        35              40              45
      Thr Xaa Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val
        50              55              60
50     Gln Asp Tyr Ile Lys Asp Met Lys
        65              70

55     <210> 27
      <211> 143
      <212> PRT
      <213> Unknown

      <220>

60     <223> Description of Unknown Organism:primate

      <400> 27
      Met Lys Ile Ser Val Ala Ala Ile Pro Phe Phe Leu Leu Ile Thr Ile
        1              5              10              15

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SUBSTITUTE SHEET (rule 26)

5 Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
20 25 30

Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
35 40 45

10 Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
50 55 60

Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65 70 75 80

15 Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn Thr Lys Thr
85 90 95

20 Glu Ser Ser Ser Arg Gly Pro Tyr His Pro Ser Glu Cys Cys Phe Thr
100 105 110

Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu
115 120 125

25 Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile Thr Xaa
130 135 140

<210> 28
<211> 93
<212> PRT
<213> Unknown

<220>
<223> Description of Unknown Organism:primate

<400> 28
Met Lys Ile Ser Val Ala Ala Ile Pro Phe Phe Leu Leu Ile Thr Ile
1 5 10 15

40 Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
20 25 30

Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
35 40 45

Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
50 55 60

50 Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65 70 75 80

Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
85 90

55 <210> 29
<211> 93
<212> PRT
<213> Unknown

60 <220>
<223> Description of Unknown Organism:primate
<400> 29

BNSDOCID: <WO 0001817A2 | >

38

5 Met Lys Ile Ser Val Ala Ala Ile Pro Phe Phe Leu Leu Ile Thr Ile
 1 5 10 15
 Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
 20 25 30
 10 Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
 35 40 45
 Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
 50 55 60
 15 Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
 65 70 75 80
 20 Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
 85 90
 <210> 30
 <211> 93
 25 <212> PRT
 <213> Unknown
 <220>
 <223> Description of Unknown Organism:primate
 30 <400> 30
 Met Lys Ile Ser Val Ala Ala Ile Pro Phe Phe Leu Leu Ile Thr Ile
 1 5 10 15
 35 Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
 20 25 30
 Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
 35 40 45
 40 Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
 50 55 60
 45 Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
 65 70 75 80
 Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
 85 90
 50 <210> 31
 <211> 1082
 <212> DNA
 <213> Unknown
 55 <220>
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 60 <221> CDS
 <222> (1)..(1080)
 <220>
 <221> misc_feature

SUBSTITUTE SHEET (rule 26)

5 <222> (20)
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 10 <223> nucleotide may be A, C, G or T
 <220>
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 15 <223> nucleotide may be A, C, G, or T
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 20 <223> nucleotide may be C or T
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 25 <223> nucleotide may be A or C
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 30 <223> nucleotide may be C or G
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 Met Pro Phe Pro Gly Pro His Ala Gly Arg Ser Ser Thr Leu Lys Asp
 35 1 5 10 15
 acc acc cct cca tcc cac caa ata ttt gga agg ctc ctg gaa gat ctc 96
 Thr Thr Pro Pro Ser His Gln Ile Phe Gly Arg Leu Leu Glu Asp Leu
 20 25 30
 40 caa atc caa gtg tct ccc act gcc cac ggc att cca gac act ttt gac 144
 Gln Ile Gln Val Ser Pro Thr Ala His Gly Ile Pro Asp Thr Phe Asp
 35 40 45
 45 cct tac ctg gac atc gcc ctg gat atc cag gca gct cag agt gtc cag 192
 Pro Tyr Leu Asp Ile Ala Leu Asp Ile Gln Ala Ala Gln Ser Val Gln
 50 55 60
 caa gct ttg gaa cag ttg gtg aag ccc gaa gaa ctc aat gga gag aat 240
 Gln Ala Leu Glu Gln Leu Val Lys Pro Glu Glu Leu Asn Gly Glu Asn
 65 70 75 80
 gcc tat cat tgt ggt ctt tgt ctc cag agg gcg ccg gcc tcc aag acg 288
 Ala Tyr His Cys Gly Leu Cys Leu Gln Arg Ala Pro Ala Ser Lys Thr
 85 90 95
 55 tta act tta cac acc tct gcc aag gtc ctc atc ctt gtc ttg aag aga 336
 Leu Thr Leu His Thr Ser Ala Lys Val Leu Ile Leu Val Leu Lys Arg
 100 105 110
 60 ttc tcc gat gtc aca ggc aac aag att gcc aag aat gtg caa tat cct 384
 Phe Ser Asp Val Thr Gly Asn Lys Ile Ala Lys Asn Val Gln Tyr Pro
 115 120 125

SUBSTITUTE SHEET (rule 26)

40

5	gag tgc ctt gac atg cag cca tac atg tct cag cag aac aca gga cct Glu Cys Leu Asp Met Gln Pro Tyr Met Ser Gln Gln Asn Thr Gly Pro 130 135 140	432
10	ctt gtc tat gtc ctc tat gct gtg ctg gtc cac gct ggg tgg agt tgt Leu Val Tyr Val Leu Tyr Ala Val Leu Val His Ala Gly Trp Ser Cys 145 150 155 160	480
15	cac aac gga cat tac ttc tct tat gtc aaa gct caa gaa ggc cag tgg His Asn Gly His Tyr Phe Ser Tyr Val Lys Ala Gln Glu Gly Gln Trp 165 170 175	528
20	tat aaa atg gat gat gcc gag gtc acc gcc tct agc atc act tct gtc Tyr Lys Met Asp Asp Ala Glu Val Thr Ala Ser Ser Ile Thr Ser Val 180 185 190	576
25	ctg agt caa cag gcc tac gtc ctc ttt tac atc cag aag agt gaa tgg Leu Ser Gln Gln Ala Tyr Val Leu Phe Tyr Ile Gln Lys Ser Glu Trp 195 200 205	624
30	gaa aga cac agt gag agt gtg tca aga ggc agg gaa cca aga gcc ctt Glu Arg His Ser Glu Ser Val Ser Arg Gly Arg Glu Pro Arg Ala Leu 210 215 220	672
35	ggc gca gaa gac aca gac agg cga gca acg caa gga gag ctc aag aga Gly Ala Glu Asp Thr Asp Arg Arg Ala Thr Gln Gly Glu Leu Lys Arg 225 230 235 240	720
40	gac cac ccc tgc ctc cag gcc ccc gag ttg gac gag cac ttg gtg gaa Asp His Pro Cys Leu Gln Ala Pro Glu Leu Asp Glu His Leu Val Glu 245 250 255	768
45	aga gcc act cag gaa agc acc tta gac cac tgg aaa ttc ctt caa gag Arg Ala Thr Gln Glu Ser Thr Leu Asp His Trp Lys Phe Leu Gln Glu 260 265 270	816
50	caa aac aaa acg aag cct gag ttc aac gtc aga aaa gtc gaa ggt acc Gln Asn Lys Thr Lys Pro Glu Phe Asn Val Arg Lys Val Glu Gly Thr 275 280 285	864
55	ctg cct ccc gac gta ctt gtg att cat caa tca aaa tac aag tgt ggg Leu Pro Pro Asp Val Leu Val Ile His Gln Ser Lys Tyr Lys Cys Gly 290 295 300	912
60	atg aag aac cat cat cct gaa cag caa agc tcc ctg cta aac ctc tct Met Lys Asn His His Pro Glu Gln Gln Ser Ser Leu Leu Asn Leu Ser 305 310 315 320	960
65	tcg acg acc ccg aca cat cag gag tcc atg aac act ggc aca ctc gct Ser Thr Thr Pro Thr His Gln Glu Ser Met Asn Thr Gly Thr Leu Ala 325 330 335	1008
70	tcc ctg cga ggg agg gcc agg aga tcc aaa ggg aag aac aaa cac agc Ser Leu Arg Gly Arg Ala Arg Arg Ser Lys Gly Lys Asn Lys His Ser 340 345 350	1056
75	aag agg gct ctg ctt gtg tgc cag tg Lys Arg Ala Leu Leu Val Cys Gln 355 360	1082

SUBSTITUTE SHEET (rule 26)

41

5 <210> 32
 <211> 360
 <212> PRT
 <213> Unknown

 <400> 32
 10 Met Pro Phe Pro Gly Pro His Ala Gly Arg Ser Ser Thr Leu Lys Asp
 1 5 10 15
 Thr Thr Pro Pro Ser His Gln Ile Phe Gly Arg Leu Leu Glu Asp Leu
 20 25 30
 15 Gln Ile Gln Val Ser Pro Thr Ala His Gly Ile Pro Asp Thr Phe Asp
 35 40 45
 Pro Tyr Leu Asp Ile Ala Leu Asp Ile Gln Ala Ala Gln Ser Val Gln
 20 50 55 60
 Gln Ala Leu Glu Gln Leu Val Lys Pro Glu Glu Leu Asn Gly Glu Asn
 65 70 75 80
 25 Ala Tyr His Cys Gly Leu Cys Leu Gln Arg Ala Pro Ala Ser Lys Thr
 85 90 95
 Leu Thr Leu His Thr Ser Ala Lys Val Leu Ile Leu Val Leu Lys Arg
 100 105 110
 30 Phe Ser Asp Val Thr Gly Asn Lys Ile Ala Lys Asn Val Gln Tyr Pro
 115 120 125
 Glu Cys Leu Asp Met Gln Pro Tyr Met Ser Gln Gln Asn Thr Gly Pro
 35 130 135 140
 Leu Val Tyr Val Leu Tyr Ala Val Leu Val His Ala Gly Trp Ser Cys
 145 150 155 160
 40 His Asn Gly His Tyr Phe Ser Tyr Val Lys Ala Gln Glu Gly Gln Trp
 165 170 175
 Tyr Lys Met Asp Asp Ala Glu Val Thr Ala Ser Ser Ile Thr Ser Val
 180 185 190
 45 Leu Ser Gln Gln Ala Tyr Val Leu Phe Tyr Ile Gln Lys Ser Glu Trp
 195 200 205
 Glu Arg His Ser Glu Ser Val Ser Arg Gly Arg Glu Pro Arg Ala Leu
 50 210 215 220
 Gly Ala Glu Asp Thr Asp Arg Arg Ala Thr Gln Gly Glu Leu Lys Arg
 225 230 235 240
 55 Asp His Pro Cys Leu Gln Ala Pro Glu Leu Asp Glu His Leu Val Glu
 245 250 255
 Arg Ala Thr Gln Glu Ser Thr Leu Asp His Trp Lys Phe Leu Gln Glu
 260 265 270
 60 Gln Asn Lys Thr Lys Pro Glu Phe Asn Val Arg Lys Val Glu Gly Thr
 275 280 285

SUBSTITUTE SHEET (rule 26)

42

5 Leu Pro Pro Asp Val Leu Val Ile His Gln Ser Lys Tyr Lys Cys Gly
 290 295 300
 Met Lys Asn His His Pro Glu Gln Gln Ser Ser Leu Leu Asn Leu Ser
 305 310 315 320
 10 Ser Thr Thr Pro Thr His Gln Glu Ser Met Asn Thr Gly Thr Leu Ala
 325 330 335
 Ser Leu Arg Gly Arg Ala Arg Arg Ser Lys Gly Lys Asn Lys His Ser
 340 345 350
 15 Lys Arg Ala Leu Leu Val Cys Gln
 355 360
 20 <210> 33
 <211> 1683
 <212> DNA
 <213> Unknown
 25 <220>
 <223> Description of Unknown Organism: primate
 <220>
 <221> CDS
 30 <222> (1)..(1590)
 <400> 33
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 Met Glu Asp Asp Ser Leu Tyr Leu Gly Gly Glu Trp Gln Phe Asn His
 35 1 5 10 15
 ttt tca aaa ctc aca tct tct cgg cca gat gca gct ttt gct gaa atc 96
 Phe Ser Lys Leu Thr Ser Ser Arg Pro Asp Ala Ala Phe Ala Glu Ile
 20 25 30
 40 cag cgg act tct ctc cct gag aag tca cca ctc tca tct gag gcc cgt 144
 Gln Arg Thr Ser Leu Pro Glu Lys Ser Pro Leu Ser Ser Glu Ala Arg
 35 40 45
 45 gtc gac ctc tgt gat gat ttg gct cct gtg gca aga cag ctt gct ccc 192
 Val Asp Leu Cys Asp Asp Leu Ala Pro Val Ala Arg Gln Leu Ala Pro
 50 55 60
 agg gag aag ctt cct ctg agt agc agg aga cct gct gcg gtg ggg gct 240
 Arg Glu Lys Leu Pro Leu Ser Ser Arg Arg Pro Ala Ala Val Gly Ala
 65 70 75 80
 ggg ctc cag aat atg gga aat acc tgc tac gag aac gct tcc ctg cag 288
 Gly Leu Gln Asn Met Gly Asn Thr Cys Tyr Glu Asn Ala Ser Leu Gln
 85 90 95
 tgc ctg aca tac aca ccg ccc ctt gcc aac tac atg ctg tcc cgg gag 336
 Cys Leu Thr Tyr Thr Pro Pro Leu Ala Asn Tyr Met Leu Ser Arg Glu
 100 105 110
 60 cac tct caa aca tgt cag cgt ccc aag tgc tgc atg ctc tgt act atg 384
 His Ser Gln Thr Cys Gln Arg Pro Lys Cys Cys Met Leu Cys Thr Met
 115 120 125

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43

5	caa gct cac atc aca tgg gcc ctc cac agt cct ggt cat gtc atc cag	432
	Gln Ala His Ile Thr Trp Ala Leu His Ser Pro Gly His Val Ile Gln	
	130 135 140	
10	ccc tca cag gca ttg gct gct ggc ttc cat aga ggc aag cag gaa gat	480
	Pro Ser Gln Ala Leu Ala Ala Gly Phe His Arg Gly Lys Gln Glu Asp	
	145 150 155 160	
15	gcc cat gaa ttt ctc atg ttc act gtg gat gcc atg aaa aag gca tgc	528
	Ala His Glu Phe Leu Met Phe Thr Val Asp Ala Met Lys Lys Ala Cys	
	165 170 175	
20	ctt ccc ggc cac aag cag gta gat cat cac tct aag gac acc acc ctc	576
	Leu Pro Gly His Lys Gln Val Asp His His Ser Lys Asp Thr Thr Leu	
	180 185 190	
25	atc cac caa ata ttt gga ggc tgc tgg aga tct caa atc aag tgt ctc	624
	Ile His Gln Ile Phe Gly Gly Cys Trp Arg Ser Gln Ile Lys Cys Leu	
	195 200 205	
30	cac tgc cac ggg att cca gac act ttt gac cct tac ctg gac atc gcc	672
	His Cys His Gly Ile Pro Asp Thr Phe Asp Pro Tyr Leu Asp Ile Ala	
	210 215 220	
35	ctg gat atc cag gca gct cag agt gtc aag caa gct ttg gaa cag ttg	720
	Leu Asp Ile Gln Ala Ala Gln Ser Val Lys Gln Ala Leu Glu Gln Leu	
	225 230 235 240	
40	gtg aag ccc gaa gaa ctc aat gga gag aat gcc tat cat tgt ggt ctt	768
	Val Lys Pro Glu Glu Leu Asn Gly Glu Asn Ala Tyr His Cys Gly Leu	
	245 250 255	
45	tgt ctc cag agg gcg ccg gcc tcc aag acg tta act tta cac act tct	816
	Cys Leu Gln Arg Ala Pro Ala Ser Lys Thr Leu Thr Leu His Thr Ser	
	260 265 270	
50	gcc aag gtc ctc atc ctt gtm ttg aag aga ttc tcc gat gtc aca ggc	864
	Ala Lys Val Leu Ile Leu Xaa Leu Lys Arg Phe Ser Asp Val Thr Gly	
	275 280 285	
55	aac aaa ctt gcc aag aat gtg caa tat cct gag tgc ctt gac atg cag	912
	Asn Lys Leu Ala Lys Asn Val Gln Tyr Pro Glu Cys Leu Asp Met Gln	
	290 295 300	
60	cca tac atg tct cag cag aac aca gga cct ctt gtc tat gtc ctc tat	960
	Pro Tyr Met Ser Gln Gln Asn Thr Gly Pro Leu Val Tyr Val Leu Tyr	
	305 310 315 320	
65	gct gtg ctg gtc cac gct ggg tgg agt tgt cac aac gga cat tac ttc	1008
	Ala Val Leu Val His Ala Gly Trp Ser Cys His Asn Gly His Tyr Phe	
	325 330 335	
70	tct tat gtc aaa gct caa gaa ggc cag tgg tat aaa atg gat gat gcc	1056
	Ser Tyr Val Lys Ala Gln Glu Gly Gln Trp Tyr Lys Met Asp Asp Ala	
	340 345 350	
75	gag gtc acc gcc tct agc atc act tct gtc ctg agt caa cag gcc tac	1104
	Glu Val Thr Ala Ser Ser Ile Thr Ser Val Leu Ser Gln Gln Ala Tyr	
	355 360 365	

SUBSTITUTE SHEET (rule 26)

44

5	gtc ctc ttt tac atc cag aag agt gaa tgg gaa aga cac agt gag agt	1152
	Val Leu Phe Tyr Ile Gln Lys Ser Glu Trp Glu Arg His Ser Glu Ser	
	370 375 380	
10	gtg tca aga ggc agg gaa cca aga gcc ctt ggc gca gaa gac aca gac	1200
	Val Ser Arg Gly Arg Glu Pro Arg Ala Leu Gly Ala Glu Asp Thr Asp	
	385 390 395 400	
15	agg cga gca acg caa gga gag ctc aag aga gac cac ccc tgc ctc cag	1248
	Arg Arg Ala Thr Gln Gly Glu Leu Lys Arg Asp His Pro Cys Leu Gln	
	405 410 415	
20	gcc ccc gag ttg gac gag cac ttg gtg gaa aga gcc act cag gaa agc	1296
	Ala Pro Glu Leu Asp Glu His Leu Val Glu Arg Ala Thr Gln Glu Ser	
	420 425 430	
25	acc tta gac cac tgg aaa ttc ctt caa gag caa aac aaa acg aag cct	1344
	Thr Leu Asp His Trp Lys Phe Leu Gln Glu Gln Asn Lys Thr Lys Pro	
	435 440 445	
30	gag ttc aac gtc aga aaa gtc gaa ggt acc ctg cct ccc gac gta ctt	1392
	Glu Phe Asn Val Arg Lys Val Glu Gly Thr Leu Pro Pro Asp Val Leu	
	450 455 460	
35	gtg att cat caa tca aaa tac aag tgt ggg atg aag aac cat cat cct	1440
	Val Ile His Gln Ser Lys Tyr Lys Cys Gly Met Lys Asn His His Pro	
	465 470 475 480	
40	gaa cag caa agc tcc ctg cta aac ctc tct tct acg acc ccg aca cat	1488
	Glu Gln Gln Ser Ser Leu Leu Asn Leu Ser Ser Thr Thr Pro Thr His	
	485 490 495	
45	cag gag tcc atg aac act ggc aca ctc gct tcc ctg cga ggg agg gcc	1536
	Gln Glu Ser Met Asn Thr Gly Thr Leu Ala Ser Leu Arg Gly Arg Ala	
	500 505 510	
50	agg aga tcc aaa ggg aag aac aaa cac agc aag agg gct ctg ctt gtg	1584
	Arg Arg Ser Lys Gly Lys Asn Lys His Ser Lys Arg Ala Leu Leu Val	
	515 520 525	
55	tgc cag tgatctcagt ggaagtaccg acccacacgt aggggtgcac acacacacgc	1640
	Cys Gln	
	530	
60	acacacacag acacacacat aactacaccc agaagcgcgc tga	1683
	<210> 34	
	<211> 530	
	<212> PRT	
	<213> Unknown	
55	<400> 34	
	Met Glu Asp Asp Ser Leu Tyr Leu Gly Gly Glu Trp Gln Phe Asn His	
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60	Phe Ser Lys Leu Thr Ser Ser Arg Pro Asp Ala Ala Phe Ala Glu Ile	
	20 25 30	
	Gln Arg Thr Ser Leu Pro Glu Lys Ser Pro Leu Ser Ser Glu Ala Arg	
	35 40 45	

SUBSTITUTE SHEET (rule 26)

45

5	Val	Asp	Leu	Cys	Asp	Asp	Leu	Ala	Pro	Val	Ala	Arg	Gln	Leu	Ala	Pro
	50						55					60				
	Arg	Glu	Lys	Leu	Pro	Leu	Ser	Ser	Arg	Arg	Pro	Ala	Ala	Val	Gly	Ala
	65					70					75					80
10	Gly	Leu	Gln	Asn	Met	Gly	Asn	Thr	Cys	Tyr	Glu	Asn	Ala	Ser	Leu	Gln
					85					90					95	
	Cys	Leu	Thr	Tyr	Thr	Pro	Pro	Leu	Ala	Asn	Tyr	Met	Leu	Ser	Arg	Glu
				100					105					110		
15	His	Ser	Gln	Thr	Cys	Gln	Arg	Pro	Lys	Cys	Cys	Met	Leu	Cys	Thr	Met
			115					120					125			
	Gln	Ala	His	Ile	Thr	Trp	Ala	Leu	His	Ser	Pro	Gly	His	Val	Ile	Gln
20		130					135					140				
	Pro	Ser	Gln	Ala	Leu	Ala	Gly	Phe	His	Arg	Gly	Lys	Gln	Glu	Asp	
	145					150				155					160	
25	Ala	His	Glu	Phe	Leu	Met	Phe	Thr	Val	Asp	Ala	Met	Lys	Lys	Ala	Cys
					165					170					175	
	Leu	Pro	Gly	His	Lys	Gln	Val	Asp	His	His	Ser	Lys	Asp	Thr	Thr	Leu
30				180					185					190		
	Ile	His	Gln	Ile	Phe	Gly	Gly	Cys	Trp	Arg	Ser	Gln	Ile	Lys	Cys	Leu
			195					200					205			
	His	Cys	His	Gly	Ile	Pro	Asp	Thr	Phe	Asp	Pro	Tyr	Leu	Asp	Ile	Ala
35		210					215					220				
	Leu	Asp	Ile	Gln	Ala	Ala	Gln	Ser	Val	Lys	Gln	Ala	Leu	Glu	Gln	Leu
	225					230					235					240
40	Val	Lys	Pro	Glu	Glu	Leu	Asn	Gly	Glu	Asn	Ala	Tyr	His	Cys	Gly	Leu
				245						250					255	
	Cys	Leu	Gln	Arg	Ala	Pro	Ala	Ser	Lys	Thr	Leu	Thr	Leu	His	Thr	Ser
				260					265					270		
45	Ala	Lys	Val	Leu	Ile	Leu	Xaa	Leu	Lys	Arg	Phe	Ser	Asp	Val	Thr	Gly
			275					280					285			
	Asn	Lys	Leu	Ala	Lys	Asn	Val	Gln	Tyr	Pro	Glu	Cys	Leu	Asp	Met	Gln
50		290					295					300				
	Pro	Tyr	Met	Ser	Gln	Gln	Asn	Thr	Gly	Pro	Leu	Val	Tyr	Val	Leu	Tyr
	305					310					315					320
55	Ala	Val	Leu	Val	His	Ala	Gly	Trp	Ser	Cys	His	Asn	Gly	His	Tyr	Phe
					325					330					335	
	Ser	Tyr	Val	Lys	Ala	Gln	Glu	Gly	Gln	Trp	Tyr	Lys	Met	Asp	Asp	Ala
				340					345					350		
60	Glu	Val	Thr	Ala	Ser	Ser	Ile	Thr	Ser	Val	Leu	Ser	Gln	Gln	Ala	Tyr
			355					360					365			

SUBSTITUTE SHEET (rule 26)

46

5 Val Leu Phe Tyr Ile Gln Lys Ser Glu Trp Glu Arg His Ser Glu Ser
 370 375 380
 Val Ser Arg Gly Arg Glu Pro Arg Ala Leu Gly Ala Glu Asp Thr Asp
 385 390 395 400
 10 Arg Arg Ala Thr Gln Gly Glu Leu Lys Arg Asp His Pro Cys Leu Gln
 405 410 415
 Ala Pro Glu Leu Asp Glu His Leu Val Glu Arg Ala Thr Gln Glu Ser
 420 425 430
 15 Thr Leu Asp His Trp Lys Phe Leu Gln Glu Gln Asn Lys Thr Lys Pro
 435 440 445
 Glu Phe Asn Val Arg Lys Val Glu Gly Thr Leu Pro Pro Asp Val Leu
 450 455 460
 20 Val Ile His Gln Ser Lys Tyr Lys Cys Gly Met Lys Asn His His Pro
 465 470 475 480
 25 Glu Gln Gln Ser Ser Leu Leu Asn Leu Ser Ser Thr Thr Pro Thr His
 485 490 495
 Gln Glu Ser Met Asn Thr Gly Thr Leu Ala Ser Leu Arg Gly Arg Ala
 500 505 510
 30 Arg Arg Ser Lys Gly Lys Asn Lys His Ser Lys Arg Ala Leu Leu Val
 515 520 525
 35 Cys Gln
 530
 40 <210> 35
 <211> 735
 <212> DNA
 <213> Unknown
 45 <220>
 <223> Description of Unknown Organism:primate
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 <222> (1)..(735)
 50 <220>
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 <222> (197)
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 55 <220>
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 <222> (590)
 <223> nucleotide may be A, C, G, or T
 60 <220>
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 <222> (664)
 <223> nucleotide may be A, C, G, or T

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5 <220>
 <221> misc_feature
 <222> (665)
 <223> nucleotide may be A, C, G, or T

10 <220>
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 <222> (666)
 <223> nucleotide may be A, C, G, or T

15 <220>
 <221> misc_feature
 <222> (708)
 <223> nucleotide may be A, C, G, or T

20 <220>
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 <222> (715)
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 Met Ala Val Pro Ser Trp Ile Val Lys Arg Arg Leu Leu Pro Trp Ser
 1 5 10 15

30 atc aaa ttt ttg gag ggt atc tca gat cac ggc gtg aag tgc tcc gtg 96
 Ile Lys Phe Leu Glu Gly Ile Ser Asp His Gly Val Lys Cys Ser Val
 20 25 30

35 tgc aag agc gtc tcg gac acc tac gac ccc tac ttg gac gtc gcg ctg 144
 Cys Lys Ser Val Ser Asp Thr Tyr Asp Pro Tyr Leu Asp Val Ala Leu
 35 40 45

40 gag atc cgg caa gct gcg aat att gtg cgt gct ctg gaa ctt ttt gtg 192
 Glu Ile Arg Gln Ala Ala Asn Ile Val Arg Ala Leu Glu Leu Phe Val
 50 55 60

45 aaa gca gat gtc ctg agt gga gag aat gcc tac atg tgt gct aaa tgc 240
 Lys Ala Asp Val Leu Ser Gly Glu Asn Ala Tyr Met Cys Ala Lys Cys
 65 70 75 80

50 aag aag aag gtt cca gcc agc aag cgc ttc acc atc cac aga aca tcc 288
 Lys Lys Lys Val Pro Ala Ser Lys Arg Phe Thr Ile His Arg Thr Ser
 85 90 95

55 aac gtc tta acc ctt tcc ctc aag cgc ttt gcc aac ttc agc ggg ggg 336
 Asn Val Leu Thr Leu Ser Leu Lys Arg Phe Ala Asn Phe Ser Gly Gly
 100 105 110

60 aag atc acc aag gat gta ggc tat ccg gaa ttc ctc aac ata cgt ccg 384
 Lys Ile Thr Lys Asp Val Gly Tyr Pro Glu Phe Leu Asn Ile Arg Pro
 115 120 125

65 tat atg tcc cag aat aat ggt gat cct gtc atg tat gga ctc tat gct 432
 Tyr Met Ser Gln Asn Asn Gly Asp Pro Val Met Tyr Gly Leu Tyr Ala
 130 135 140

70 gtc ctg gtg cac tcg ggc tac agc tgc cat gcc ggg cac tat tac tgc 480
 Val Leu Val His Ser Gly Tyr Ser Cys His Ala Gly His Tyr Tyr Cys
 145 150 155 160

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5	tac	gtg	aag	gca	agc	aat	gga	cag	tgg	tac	cag	atg	aat	gat	tcc	ttg	528
	Tyr	Val	Lys	Ala	Ser	Asn	Gly	Gln	Trp	Tyr	Gln	Met	Asn	Asp	Ser	Leu	
					165					170					175		
10	gtc	cca	ttc	cag	caa	cgt	cca	agt	tgg	ttt	ctg	aaa	cca	gca	ggc	cta	576
	Val	Pro	Phe	Gln	Gln	Arg	Pro	Ser	Trp	Phe	Leu	Lys	Pro	Ala	Gly	Leu	
				180					185					190			
15	agt	ggc	ttg	ttc	tca	tcg	gcg	aat	ttc	cag	gct	ctc	aag	aaa	aat	tcc	624
	Ser	Gly	Leu	Phe	Ser	Ser	Ala	Asn	Phe	Gln	Ala	Leu	Lys	Lys	Asn	Ser	
			195					200					205				
20	cga	agg	gcc	tcc	att	ttc	cag	gaa	cag	gtt	cct	tcc	tcc	cct	tcc	cgg	672
	Arg	Arg	Ala	Ser	Ile	Phe	Gln	Glu	Gln	Val	Pro	Ser	Ser	Pro	Ser	Arg	
			210				215					220					
25	aat	ggg	gat	tat	ttt												735
	Asn	Gly	Asp	Tyr	Phe												
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	1				5					10					15		
40	Ile	Lys	Phe	Leu	Glu	Gly	Ile	Ser	Asp	His	Gly	Val	Lys	Cys	Ser	Val	
				20					25					30			
45	Cys	Lys	Ser	Val	Ser	Asp	Thr	Tyr	Asp	Pro	Tyr	Leu	Asp	Val	Ala	Leu	
			35					40					45				
50	Glu	Ile	Arg	Gln	Ala	Ala	Asn	Ile	Val	Arg	Ala	Leu	Glu	Leu	Phe	Val	
		50					55					60					
55	Lys	Ala	Asp	Val	Leu	Ser	Gly	Glu	Asn	Ala	Tyr	Met	Cys	Ala	Lys	Cys	
	65					70					75					80	
60	Lys	Lys	Lys	Val	Pro	Ala	Ser	Lys	Arg	Phe	Thr	Ile	His	Arg	Thr	Ser	
				85						90				95			
65	Asn	Val	Leu	Thr	Leu	Ser	Leu	Lys	Arg	Phe	Ala	Asn	Phe	Ser	Gly	Gly	
			100						105					110			
70	Lys	Ile	Thr	Lys	Asp	Val	Gly	Tyr	Pro	Glu	Phe	Leu	Asn	Ile	Arg	Pro	
			115					120					125				
75	Tyr	Met	Ser	Gln	Asn	Asn	Gly	Asp	Pro	Val	Met	Tyr	Gly	Leu	Tyr	Ala	
		130					135					140					
80	Val	Leu	Val	His	Ser	Gly	Tyr	Ser	Cys</								

BNSDOCID: <WO 0001817A2 1 >

49

5 Tyr Val Lys Ala Ser Asn Gly Gln Trp Tyr Gln Met Asn Asp Ser Leu
165 170 175

Val Pro Phe Gln Gln Arg Pro Ser Trp Phe Leu Lys Pro Ala Gly Leu
180 185 190

10 Ser Gly Leu Phe Ser Ser Ala Asn Phe Gln Ala Leu Lys Lys Asn Ser
195 200 205

Arg Arg Ala Ser Ile Phe Gln Glu Gln Val Pro Ser Ser Pro Ser Arg
210 215 220

15 Ala Ala Arg Ile Val Asn Ser Arg Phe Ile Pro Ser Arg Asn Leu Gly
225 230 235 240

20 Asn Gly Asp Tyr Phe
245

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25 <212> DNA
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Met Gln Lys Ala Cys Leu Asn Gly Cys Ala Lys Leu Asp Arg Gln Thr
1 5 10 15

40 cag gct act acc ttg gtc cat caa att ttt gga ggg tat ctc aga tca 96
Gln Ala Thr Thr Leu Val His Gln Ile Phe Gly Gly Tyr Leu Arg Ser
20 25 30

45 cgc gtg aag tgc tcc gtg tgc aag agc gtc tcg gac acc tac gac ccc 144
Arg Val Lys Cys Ser Val Cys Lys Ser Val Ser Asp Thr Tyr Asp Pro
35 40 45

50 tac ttg gac gtc gcg ctg gag atc cgg caa gct gcg aat att gtg cgt 192
Tyr Leu Asp Val Ala Leu Glu Ile Arg Gln Ala Ala Asn Ile Val Arg
50 55 60

gct ctg gaa ctt ttt gtg aaa gca gat gtc ctg agt gga gag aat gcc 240
Ala Leu Glu Leu Phe Val Lys Ala Asp Val Leu Ser Gly Glu Asn Ala
65 70 75 80

55 tac atg tgt gct aaa tgc aag aag aag gtt cca gcc agc aag cgc ttc 288
Tyr Met Cys Ala Lys Cys Lys Lys Lys Val Pro Ala Ser Lys Arg Phe
85 90 95

60 acc atc cac aga aca tcc aac gtc tta acc ctt tcc ctc aag cgc ttt 336
Thr Ile His Arg Thr Ser Asn Val Leu Thr Leu Ser Leu Lys Arg Phe
100 105 110

gcc aac ttc agc ggg ggg aag atc acc aag gat gta ggc tat ccg gaa 384

SUBSTITUTE SHEET (rule 26)

50

5	Ala Asn Phe Ser Gly Gly Lys Ile Thr Lys Asp Val Gly Tyr Pro Glu	115	120	125	
	ttc ctc aac ata cgt ccg tat atg tcc cag aat 'aat ggt gat cct gtc				432
	Phe Leu Asn Ile Arg Pro Tyr Met Ser Gln Asn Asn Gly Asp Pro Val	130	135	140	
10	atg tat gga ctc tat gct gtc ctg gtg cac tcg ggc tac agc tgc cat				480
	Met Tyr Gly Leu Tyr Ala Val Leu Val His Ser Gly Tyr Ser Cys His	145	150	155	160
15	gcc ggg cac tat tac tgc tac gtg aag gca agc aat gga cag tgg tac				528
	Ala Gly His Tyr Tyr Cys Tyr Val Lys Ala Ser Asn Gly Gln Trp Tyr	165	170		175
20	cag atg aat gat tcc ttg gtc cat tcc agc aac gtc aag gtg gtt ctg				576
	Gln Met Asn Asp Ser Leu Val His Ser Ser Asn Val Lys Val Val Leu	180	185	190	
25	aac cag cag gcc tac gtg ctg ttc tat ctg cga att cca ggc tct aag				624
	Asn Gln Gln Ala Tyr Val Leu Phe Tyr Leu Arg Ile Pro Gly Ser Lys	195	200	205	
30	aaa agt ccc gag ggc ctc atc tcc agg aca ggc tcc tcc tcc ctt ccc				672
	Lys Ser Pro Glu Gly Leu Ile Ser Arg Thr Gly Ser Ser Ser Leu Pro	210	215	220	
	ggc cgc ccg agt gtg att cca gat cac tcc aag aag aac atc ggc aat				720
	Gly Arg Pro Ser Val Ile Pro Asp His Ser Lys Lys Asn Ile Gly Asn	225	230	235	240
35	ggg att att tcc tcc cca ctg act gga aag cga caa gac tct ggg acg				768
	Gly Ile Ile Ser Ser Pro Leu Thr Gly Lys Arg Gln Asp Ser Gly Thr	245	250	255	
40	atg aag aag ccg cac acc act gaa gag att ggt gtg ccc ata tcc agg				816
	Met Lys Lys Pro His Thr Thr Glu Glu Ile Gly Val Pro Ile Ser Arg	260	265	270	
45	aat ggc tcc acc ctg ggc ctg aag tcc cag aac ggc tgc att cct cca				864
	Asn Gly Ser Thr Leu Gly Leu Lys Ser Gln Asn Gly Cys Ile Pro Pro	275	280	285	
50	aag ctg ccc tcg ggg tcc cct tcc ccc aaa ctc tcc cag aca ccc aca				912
	Lys Leu Pro Ser Gly Ser Pro Ser Pro Lys Leu Ser Gln Thr Pro Thr	290	295	300	
	cac atg cca acc atc cta gac gac cct gga aag aag gtg aag aag cca				960
	His Met Pro Thr Ile Leu Asp Asp Pro Gly Lys Lys Val Lys Lys Pro	305	310	315	320
55	gct cct cca cag cac ttt tcc ccc aga act gct cag ggg ctg cct ggg				1008
	Ala Pro Pro Gln His Phe Ser Pro Arg Thr Ala Gln Gly Leu Pro Gly	325	330	335	
60	acc agc aac tcg aat agc agc aga tct ggg agc caa agg cag ggc tcc				1056
	Thr Ser Asn Ser Asn Ser Ser Arg Ser Gly Ser Gln Arg Gln Gly Ser	340	345	350	
	tgg gac agc agg gat gtt gtc ctc tct acc tca cct aag ctc ctg gct				1104

SUBSTITUTE SHEET (rule 26)

51

5	Trp	Asp	Ser	Arg	Asp	Val	Val	Leu	Ser	Thr	Ser	Pro	Lys	Leu	Leu	Ala	
			355					360					365				
	aca	gcc	act	gcc	aac	ggg	cat	ggg	ctg	aag	ggg	aac	gac	gag	agc	gct	1152
	Thr	Ala	Thr	Ala	Asn	Gly	His	Gly	Leu	Lys	Gly	Asn	Asp	Glu	Ser	Ala	
			370				375					380					
10	ggc	ctc	gac	agg	agg	ggc	tcc	agc	agc	tcc	agc	cca	gag	cac	tcg	gcc	1200
	Gly	Leu	Asp	Arg	Arg		Ser	Ser	Ser	Ser		Pro	Glu	His	Ser	Ala	
						390					395					400	
15	agc	agc	gac	tcc	acc	aag	gcc	ccc	cag	acc	ccc	agg	agt	gga	gcg	gcc	1248
	Ser	Ser	Asp	Ser	Thr	Lys	Ala	Pro	Gln	Thr	Pro	Arg	Ser	Gly	Ala	Ala	
					405					410					415		
20	cat	ctc	tgc	gat	tct	cag	gaa	acg	aac	tgt	tcc	acc	gct	ggc	cac	tcc	1296
	His	Leu	Cys	Asp	Ser	Gln	Glu	Thr	Asn	Cys	Ser	Thr	Ala	Gly	His	Ser	
				420					425					430			
25	aaa	acg	ccg	cca	agt	gga	gca	gat	tct	aag	acg	gtg	aag	ctg	aag	tcc	1344
	Lys	Thr	Pro	Pro	Ser	Gly	Ala	Asp	Ser	Lys	Thr	Val	Lys	Leu	Lys	Ser	
			435					440					445				
30	cct	gtc	ctg	agc	aac	acc	acc	act	gag	cct	gca	agc	acc	atg	tct	cct	1392
	Pro	Val	Leu	Ser	Asn	Thr	Thr	Thr	Glu	Pro	Ala	Ser	Thr	Met	Ser	Pro	
			450				455					460					
35	cca	cca	gcc	aaa	aaa	ctg	gcc	ctt	tct	gcc	aag	aag	gcc	agc	acc	ctg	1440
	Pro	Pro	Ala	Lys	Lys	Leu	Ala	Leu	Ser	Ala	Lys	Lys	Ala	Ser	Thr	Leu	
			465			470					475					480	
40	tgg	agg	gcg	acc	ggc	aat	gac	ctc	cgt	cca	cct	ccc	ccc	tca	cca	tcc	1488
	Trp	Arg	Ala	Thr	Gly	Asn	Asp	Leu	Arg	Pro	Pro	Pro	Pro	Ser	Pro	Ser	
					485					490					495		
45	tcc	gac	ctc	acc	cac	ccc	atg	aaa	acc	tct	cac	ccc	gtc	gtt	gcc	tcc	1536
	Ser	Asp	Leu	Thr	His	Pro	Met	Lys	Thr	Ser	His	Pro	Val	Val	Ala	Ser	
				500					505					510			
50	act	tgg	ccc	gtc	cat	aga	gcc	agg	gct	gtg	tca	cct	gct	ccc	caa	tca	1584
	Thr	Trp	Pro	Val	His	Arg	Ala	Arg	Ala	Val	Ser	Pro	Ala	Pro	Gln	Ser	
			515				520						525				
55	tcc	agc	cgc	ctg	caa	ccc	ccc	ttc	agc	ccc	cac	ccc	aca	ttg	ctg	tcc	1632
	Ser	Ser	Arg	Leu	Gln	Pro	Pro	Phe	Ser	Pro	His	Pro	Thr	Leu	Leu	Ser	
			530				535					540					
60	agt	acc	ccc	aag	ccc	cca	ggg	acg	tca	gaa	cca	cgg	agc	tgc	tcc	tcc	1680
	Ser	Thr	Pro	Lys	Pro	Pro	Gly	Thr	Ser	Glu	Pro	Arg	Ser	Cys	Ser	Ser	
						550					555					560	
65	atc	tcg	acg	gcg	ctg	cct	cag	gtc	aac	gag	gac	ctt	gtg	tct	ctt	cca	1728
	Ile	Ser	Thr	Ala	Leu	Pro	Gln	Val	Asn	Glu	Asp	Leu	Val	Ser	Leu	Pro	
					565					570					575		
70	cac	cag	ttg	cca	gag	gcc	agt	gag	ccc	ccc	cag	agc	ccc	tct	gag	aag	1776
	His	Gln	Leu	Pro	Glu	Ala	Ser	Glu	Pro	Pro	Gln	Ser	Pro	Ser	Glu	Lys	
				580					585					590			

SUBSTITUTE SHEET (rule 26.)

52

5	agg aaa aag acc ttt gtg gga gag ccg cag agg ctg ggc tca gag acg Arg Lys Lys Thr Phe Val Gly Glu Pro Gln Arg Leu Gly Ser Glu Thr	1824
	595 600 605	
10	cgc ctc cca cag cac atc agg gag gcc act gcg gct ccc cac ggg aag Arg Leu Pro Gln His Ile Arg Glu Ala Thr Ala Pro His Gly Lys	1872
	610 615 620	
15	agg aag agg aag aag aag aag cgc ccg gag gac aca gct gcc agc gcc Arg Lys Arg Lys Lys Lys Lys Arg Pro Glu Asp Thr Ala Ala Ser Ala	1920
	625 630 635 640	
	ctg cag gag ggg cag aca cag aga cag cct ggg agc ccc atg tac agg Leu Gln Glu Gly Gln Thr Gln Arg Gln Pro Gly Ser Pro Met Tyr Arg	1968
	645 650 655	
20	agg gag ggc cag gca cag ctg ccc gct gtc aga cgg cag gaa gat ggc Arg Glu Gly Gln Ala Gln Leu Pro Ala Val Arg Arg Gln Glu Asp Gly	2016
	660 665 670	
25	aca cag cca cag gtg aat ggc cag cag gtg gga tgt gtt acg gac ggc Thr Gln Pro Gln Val Asn Gly Gln Gln Val Gly Cys Val Thr Asp Gly	2064
	675 680 685	
30	cac cac gcg agc agc agg aag cgg agg agg aaa gga gca gaa ggt ctt His His Ala Ser Ser Arg Lys Arg Arg Arg Lys Gly Ala Glu Gly Leu	2112
	690 695 700	
35	ggt gaa gaa ggc ggc ctg cac cag gac cca ctt cgg cac agc tgc tct Gly Glu Glu Gly Gly Leu His Gln Asp Pro Leu Arg His Ser Cys Ser	2160
	705 710 715 720	
	ccc atg ggt gat ggt gat cca gag gcc atg gaa gag tct cca agg aaa Pro Met Gly Asp Gly Asp Pro Glu Ala Met Glu Glu Ser Pro Arg Lys	2208
	725 730 735	
40	aag aaa aaa aaa aaa aac tcg agg ggg ggc ccg gta Lys Lys Lys Lys Lys Asn Ser Arg Gly Gly Pro Val	2244
	740 745	
45	<210> 38 <211> 748 <212> PRT <213> Unknown	
50	<400> 38 Met Gln Lys Ala Cys Leu Asn Gly Cys Ala Lys Leu Asp Arg Gln Thr	
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55	Gln Ala Thr Thr Leu Val His Gln Ile Phe Gly Gly Tyr Leu Arg Ser	
	20 25 30	
	Arg Val Lys Cys Ser Val Cys Lys Ser Val Ser Asp Thr Tyr Asp Pro	
	35 40 45	
60	Tyr Leu Asp Val Ala Leu Glu Ile Arg Gln Ala Ala Asn Ile Val Arg	
	50 55 60	
	Ala Leu Glu Leu Phe Val Lys Ala Asp Val Leu Ser Gly Glu Asn Ala	
	65 70 75 80	

SUBSTITUTE SHEET (rule 26)

5	Tyr	Met	Cys	Ala	Lys	Cys	Lys	Lys	Lys	Val	Pro	Ala	Ser	Lys	Arg	Phe	85	90	95
	Thr	Ile	His	Arg	Thr	Ser	Asn	Val	Leu	Thr	Leu	Ser	Leu	Lys	Arg	Phe	100	105	110
10	Ala	Asn	Phe	Ser	Gly	Gly	Lys	Ile	Thr	Lys	Asp	Val	Gly	Tyr	Pro	Glu	115	120	125
	Phe	Leu	Asn	Ile	Arg	Pro	Tyr	Met	Ser	Gln	Asn	Asn	Gly	Asp	Pro	Val	130	135	140
15	Met	Tyr	Gly	Leu	Tyr	Ala	Val	Leu	Val	His	Ser	Gly	Tyr	Ser	Cys	His	145	150	155
	Ala	Gly	His	Tyr	Tyr	Cys	Tyr	Val	Lys	Ala	Ser	Asn	Gly	Gln	Trp	Tyr	165	170	175
20	Gln	Met	Asn	Asp	Ser	Leu	Val	His	Ser	Ser	Asn	Val	Lys	Val	Val	Leu	180	185	190
25	Asn	Gln	Gln	Ala	Tyr	Val	Leu	Phe	Tyr	Leu	Arg	Ile	Pro	Gly	Ser	Lys	195	200	205
	Lys	Ser	Pro	Glu	Gly	Leu	Ile	Ser	Arg	Thr	Gly	Ser	Ser	Ser	Leu	Pro	210	215	220
30	Gly	Arg	Pro	Ser	Val	Ile	Pro	Asp	His	Ser	Lys	Lys	Asn	Ile	Gly	Asn	225	230	235
	Gly	Ile	Ile	Ser	Ser	Pro	Leu	Thr	Gly	Lys	Arg	Gln	Asp	Ser	Gly	Thr	245	250	255
35	Met	Lys	Lys	Pro	His	Thr	Thr	Glu	Glu	Ile	Gly	Val	Pro	Ile	Ser	Arg	260	265	270
40	Asn	Gly	Ser	Thr	Leu	Gly	Leu	Lys	Ser	Gln	Asn	Gly	Cys	Ile	Pro	Pro	275	280	285
	Lys	Leu	Pro	Ser	Gly	Ser	Pro	Ser	Pro	Lys	Leu	Ser	Gln	Thr	Pro	Thr	290	295	300
45	His	Met	Pro	Thr	Ile	Leu	Asp	Asp	Pro	Gly	Lys	Lys	Val	Lys	Lys	Pro	305	310	315
	Ala	Pro	Pro	Gln	His	Phe	Ser	Pro	Arg	Thr	Ala	Gln	Gly	Leu	Pro	Gly	325	330	335
50	Thr	Ser	Asn	Ser	Asn	Ser	Ser	Arg	Ser	Gly	Ser	Gln	Arg	Gln	Gly	Ser	340	345	350
55	Trp	Asp	Ser	Arg	Asp	Val	Val	Leu	Ser	Thr	Ser	Pro	Lys	Leu	Leu	Ala	355	360	365
	Thr	Ala	Thr	Ala	Asn	Gly	His	Gly	Leu	Lys	Gly	Asn	Asp	Glu	Ser	Ala	370	375	380
60	Gly	Leu	Asp	Arg	Arg	Gly	Ser	Ser	Ser	Ser	Ser	Pro	Glu	His	Ser	Ala	385	390	395
																			400

SUBSTITUTE SHEET (rule 26)

5 Ser Ser Asp Ser Thr Lys Ala Pro Gln Thr Pro Arg Ser Gly Ala Ala
 405 410 415
 His Leu Cys Asp Ser Gln Glu Thr Asn Cys Ser Thr Ala Gly His Ser
 420 425 430
 10 Lys Thr Pro Pro Ser Gly Ala Asp Ser Lys Thr Val Lys Leu Lys Ser
 435 440 445
 Pro Val Leu Ser Asn Thr Thr Thr Glu Pro Ala Ser Thr Met Ser Pro
 450 455 460
 15 Pro Pro Ala Lys Lys Leu Ala Leu Ser Ala Lys Lys Ala Ser Thr Leu
 465 470 475 480
 20 Trp Arg Ala Thr Gly Asn Asp Leu Arg Pro Pro Pro Pro Ser Pro Ser
 485 490 495
 Ser Asp Leu Thr His Pro Met Lys Thr Ser His Pro Val Val Ala Ser
 500 505 510
 25 Thr Trp Pro Val His Arg Ala Arg Ala Val Ser Pro Ala Pro Gln Ser
 515 520 525
 30 Ser Ser Arg Leu Gln Pro Pro Phe Ser Pro His Pro Thr Leu Leu Ser
 530 535 540
 Ser Thr Pro Lys Pro Pro Gly Thr Ser Glu Pro Arg Ser Cys Ser Ser
 545 550 555 560
 35 Ile Ser Thr Ala Leu Pro Gln Val Asn Glu Asp Leu Val Ser Leu Pro
 565 570 575
 His Gln Leu Pro Glu Ala Ser Glu Pro Pro Gln Ser Pro Ser Glu Lys
 580 585 590
 40 Arg Lys Lys Thr Phe Val Gly Glu Pro Gln Arg Leu Gly Ser Glu Thr
 595 600 605
 45 Arg Leu Pro Gln His Ile Arg Glu Ala Thr Ala Ala Pro His Gly Lys
 610 615 620
 Arg Lys Arg Lys Lys Lys Lys Arg Pro Glu Asp Thr Ala Ala Ser Ala
 625 630 635 640
 50 Leu Gln Glu Gly Gln Thr Gln Arg Gln Pro Gly Ser Pro Met Tyr Arg
 645 650 655
 Arg Glu Gly Gln Ala Gln Leu Pro Ala Val Arg Arg Gln Glu Asp Gly
 660 665 670
 55 Thr Gln Pro Gln Val Asn Gly Gln Gln Val Gly Cys Val Thr Asp Gly
 675 680 685
 60 His His Ala Ser Ser Arg Lys Arg Arg Arg Lys Gly Ala Glu Gly Leu
 690 695 700
 Gly Glu Glu Gly Gly Leu His Gln Asp Pro Leu Arg His Ser Cys Ser
 705 710 715 720

SUBSTITUTE SHEET (rule 26)

55

5 Pro Met Gly Asp Gly Asp Pro Glu Ala Met Glu Glu Ser Pro Arg Lys
 725 730 735
 Lys Lys Lys Lys Lys Asn Ser Arg Gly Gly Pro Val
 740 745
 10 <210> 39
 <211> 526
 <212> PRT
 <213> Unknown
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 <223> Description of Unknown Organism:primate
 <400> 39
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 1 5 10 15
 Pro Asp Ala Pro Glu Leu His Gln Asp Glu Ala Gln Val Val Glu Glu
 20 25 30
 25 Leu Thr Val Asn Gly Lys His Ser Leu Ser Trp Glu Ser Pro Gln Gly
 35 40 45
 30 Pro Gly Cys Gly Leu Gln Asn Thr Gly Asn Ser Cys Tyr Leu Asn Ala
 50 55 60
 Ala Leu Gln Cys Leu Thr His Thr Pro Pro Leu Ala Asp Tyr Met Leu
 65 70 75 80
 35 Ser Gln Glu His Ser Gln Thr Cys Cys Ser Pro Glu Gly Cys Lys Leu
 85 90 95
 Cys Ala Met Glu Ala Leu Val Thr Gln Ser Leu Leu His Ser His Ser
 100 105 110
 40 Gly Asp Val Met Lys Pro Ser His Ile Leu Thr Ser Ala Phe His Lys
 115 120 125
 45 His Gln Gln Glu Asp Ala His Glu Phe Leu Met Phe Thr Leu Glu Thr
 130 135 140
 Met His Glu Ser Cys Leu Gln Val His Arg Gln Ser Lys Pro Thr Ser
 145 150 155 160
 50 Glu Asp Ser Ser Pro Ile His Asp Ile Phe Gly Gly Trp Trp Arg Ser
 165 170 175
 Gln Ile Lys Cys Leu Leu Cys Gln Gly Thr Ser Asp Thr Tyr Asp Arg
 180 185 190
 55 Phe Leu Asp Ile Pro Leu Asp Ile Ser Ser Ala Gln Ser Val Lys Gln
 195 200 205
 60 Ala Leu Trp Asp Thr Glu Lys Ser Glu Glu Leu Cys Gly Asp Asn Ala
 210 215 220
 Tyr Tyr Cys Gly Lys Cys Arg Gln Lys Met Pro Ala Ser Lys Thr Leu
 225 230 235 240

SUBSTITUTE SHEET (rule 26)

56

5	His Val His Ile	Ala Pro Lys Val Leu Met Val Val Leu Asn Arg Phe	245	250	255
	Ser Ala Phe Thr	Gly Asn Lys Leu Asp Arg Lys Val Ser Tyr Pro Glu	260	265	270
10	Phe Leu Asp Leu	Lys Pro Tyr Leu Ser Glu Pro Thr Gly Gly Pro Leu	275	280	285
	Pro Tyr Ala Leu	Tyr Ala Val Leu Val His Asp Gly Ala Thr Ser His	290	295	300
15	Ser Gly His Tyr	Phe Cys Cys Val Lys Ala Gly His Gly Lys Trp Tyr	305	310	315
	Lys Met Asp Asp	Thr Lys Val Thr Arg Cys Asp Val Thr Ser Val Leu	325	330	335
20	Asn Glu Asn Ala	Tyr Val Leu Phe Tyr Val Gln Gln Ala Asn Leu Lys	340	345	350
	Gln Val Ser Ile	Asp Met Pro Glu Gly Arg Ile Asn Glu Val Leu Asp	355	360	365
25	Pro Glu Tyr Gln	Leu Lys Lys Ser Arg Arg Lys Lys His Lys Lys Lys	370	375	380
30	Ser Pro Phe Thr	Glu Asp Leu Gly Glu Pro Cys Glu Asn Arg Asp Lys	385	390	395
	Arg Ala Ile Lys	Glu Thr Ser Leu Gly Lys Gly Lys Val Leu Gln Glu	405	410	415
35	Val Asn His Lys	Lys Ala Gly Gln Lys His Gly Asn Thr Lys Leu Met	420	425	430
	Pro Gln Lys Gln	Asn His Gln Lys Ala Gly Gln Asn Leu Arg Asn Thr	435	440	445
40	Glu Val Glu Leu	Asp Leu Pro Ala Asp Ala Ile Val Ile His Gln Pro	450	455	460
45	Arg Ser Thr Ala	Asn Trp Gly Arg Asp Ser Pro Asp Lys Glu Asn Gln	465	470	475
	Pro Leu His Asn	Ala Asp Arg Leu Leu Thr Ser Gln Gly Pro Val Asn	485	490	495
50	Thr Trp Gln Leu	Cys Arg Gln Glu Gly Arg Arg Arg Ser Lys Lys Gly	500	505	510
55	Gln Asn Lys Asn	Lys Gln Gly Gln Arg Leu Leu Leu Val Cys	515	520	525
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	<211>	545			
	<212>	PRT			
	<213>	Unknown			
	<220>				

SUBSTITUTE SHEET (rule 26)

57

5 <223> Description of Unknown Organism: primate

<400> 40

Met Val Val Ser Leu Ser Phe Pro Glu Ala Asp Pro Ala Leu Ser Ser
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10 Pro Gly Ala Gln Gln Leu His Gln Asp Glu Ala Gln Val Val Val Glu
20 25 30

Leu Thr Ala Asn Asp Lys Pro Ser Leu Ser Trp Glu Cys Pro Gln Gly
35 40 45

15 Pro Gly Cys Gly Leu Gln Asn Thr Gly Asn Ser Cys Tyr Leu Asn Ala
50 55 60

20 Ala Leu Gln Cys Leu Thr His Thr Pro Pro Leu Ala Asp Tyr Met Leu
65 70 75 80

Ser Gln Glu Tyr Ser Gln Thr Cys Cys Ser Pro Glu Gly Cys Lys Met
85 90 95

25 Cys Ala Met Glu Ala His Val Thr Gln Ser Leu Leu His Ser His Ser
100 105 110

Gly Asp Val Met Lys Pro Ser Gln Ile Leu Thr Ser Ala Phe His Lys
115 120 125

30 His Gln Gln Glu Asp Ala His Glu Phe Leu Met Phe Thr Leu Glu Thr
130 135 140

35 Met His Glu Ser Cys Leu Gln Val His Arg Gln Ser Glu Pro Thr Ser
145 150 155 160

Glu Asp Ser Ser Pro Ile His Asp Ile Phe Gly Gly Leu Trp Arg Ser
165 170 175

40 Gln Ile Lys Cys Leu His Cys Gln Gly Thr Ser Asp Thr Tyr Asp Arg
180 185 190

Phe Leu Asp Val Pro Leu Asp Ile Ser Ser Ala Gln Ser Val Asn Gln
195 200 205

45 Ala Leu Trp Asp Thr Glu Lys Ser Glu Glu Leu Arg Gly Glu Asn Ala
210 215 220

50 Tyr Tyr Cys Gly Arg Cys Arg Gln Lys Met Pro Ala Ser Lys Thr Leu
225 230 235 240

His Ile His Ser Ala Pro Lys Val Leu Leu Leu Val Leu Lys Arg Phe
245 250 255

55 Ser Ala Phe Met Gly Asn Lys Leu Asp Arg Lys Val Ser Tyr Pro Glu
260 265 270

Phe Leu Asp Leu Lys Pro Tyr Leu Ser Gln Pro Thr Gly Gly Pro Leu
275 280 285

60 Pro Tyr Ala Leu Tyr Ala Val Leu Val His Glu Gly Ala Thr Cys His
290 295 300

SUBSTITUTE SHEET (rule 26)

58

5 Ser Gly His Tyr Phe Ser Tyr Val Lys Ala Arg His Gly Ala Trp Tyr
 305 310 315 320
 Lys Met Asp Asp Thr Lys Val Thr Ser Cys Asp Val Thr Ser Val Leu
 325 330 335
 10 Asn Glu Asn Ala Tyr Val Leu Phe Tyr Val Gln Gln Thr Asp Leu Lys
 340 345 350
 Gln Val Ser Ile Asp Met Pro Glu Gly Arg Val His Glu Val Leu Asp
 355 360 365
 15 Pro Glu Tyr Gln Leu Lys Lys Ser Arg Arg Lys Lys His Lys Lys Lys
 370 375 380
 20 Ser Pro Cys Thr Glu Asp Ala Gly Glu Pro Cys Lys Asn Arg Glu Lys
 385 390 395 400
 Arg Ala Thr Lys Glu Thr Ser Leu Gly Glu Gly Lys Val Xaa Gln Glu
 405 410 415
 25 Lys Asn His Lys Lys Ala Gly Gln Lys His Glu Asn Thr Lys Leu Val
 420 425 430
 Pro Gln Glu Gln Asn His Gln Lys Leu Gly Gln Lys His Arg Ile Asn
 435 440 445
 30 Glu Ile Leu Pro Gln Glu Gln Asn His Gln Lys Ala Gly Gln Ser Leu
 450 455 460
 35 Arg Asn Thr Glu Gly Glu Leu Asp Leu Pro Ala Asp Ala Ile Val Ile
 465 470 475 480
 His Leu Leu Arg Ser Thr Glu Asn Trp Gly Arg Asp Ala Pro Asp Lys
 485 490 495
 40 Glu Asn Gln Pro Trp His Asn Ala Asp Arg Leu Leu Thr Ser Gln Asp
 500 505 510
 Pro Val Asn Thr Gly Gln Leu Cys Arg Gln Glu Gly Arg Arg Arg Ser
 515 520 525
 45 Lys Lys Gly Lys Asn Lys Asn Lys Gln Gly Gln Arg Leu Leu Leu Val
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 50 Cys
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SUBSTITUTE SHEET (rule 26)

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      <223> nucleotide may be C or T

25     <220>
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45     ctc att ttt ccc agc tgc agt gga ggc ggc ggt ggg aaa gcc tgg ccc 98
      Leu Ile Phe Pro Ser Cys Ser Gly Gly Gly Gly Gly Lys Ala Trp Pro
              15                      20                      25

50     aca cac gtg gtc tgt agc gac agc cgc ttg gaa gtg ctc tac cag agt 146
      Thr His Val Val Cys Ser Asp Ser Arg Leu Glu Val Leu Tyr Gln Ser
              30                      35                      40

55     tgc gat cca tta caa gat ttt ggc ttt tct gtt gaa aag tgt tcc aag 194
      Cys Asp Pro Leu Gln Asp Phe Gly Phe Ser Val Glu Lys Cys Ser Lys
      45                      50                      55                      60

60     caa tta aaa tca aat atc aac att aga ttt gga att att ctg aga gag 242
      Gln Leu Lys Ser Asn Ile Asn Ile Arg Phe Gly Ile Ile Leu Arg Glu
              65                      70                      75

60     gac atc aaa gag ctt ttt ctt gac cta gct ctc atg tct caa ggc tca 290
      Asp Ile Lys Glu Leu Phe Leu Asp Leu Ala Leu Met Ser Gln Gly Ser
              80                      85                      90

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SUBSTITUTE SHEET (rule 26.)

60

5 tct gtt ttg aat ttc tcc tat ccc atc tgt gag gcg gct ctg ccc aag 338
 Ser Val Leu Asn Phe Ser Tyr Pro Ile Cys Glu Ala Ala Leu Pro Lys
 95 100 105

10 ttt tct ttc tgt gga aga agg aaa gga gag cag att tac tat gct ggg 386
 Phe Ser Phe Cys Gly Arg Arg Lys Gly Glu Gln Ile Tyr Tyr Ala Gly
 110 115 120

15 cct gtc aat aat cct gaa ttt act att cct cag gga gaa tac cag gtt 434
 Pro Val Asn Asn Pro Glu Phe Thr Ile Pro Gln Gly Glu Tyr Gln Val
 125 130 135 140

20 ttg ctg gaa ctg tac act gaa aaa cgg tcc acc gtg gcc tgt gcc aat 482
 Leu Leu Glu Leu Tyr Thr Glu Lys Arg Ser Thr Val Ala Cys Ala Asn
 145 150 155

25 gct act atc atg tgc tcc tgactgtggg cctggttagca aaaactcaca 530
 Ala Thr Ile Met Cys Ser
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30 gccagctgca tctcgtcggg aaccttccaa gtcctcttga ctgaacctac tgtggggagga 590
 gaagcagctg atgacagaga gaggctctac aaagaagcgc ccccaaagag tgcagctgct 650
 aatttttagtc ccaggaccag acatcccag actccacaga tgtaatgaag tccccgaatg 710

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 ctctaattgg tcgcctccca ccagactcac ctgcttttca acttttttagg agtgcttcct 830
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 <213> Unknown

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50 Ser Cys Ser Gly Gly Gly Gly Gly Lys Ala Trp Pro Thr His Val Val
 20 25 30

55 Cys Ser Asp Ser Arg Leu Glu Val Leu Tyr Gln Ser Cys Asp Pro Leu
 35 40 45

60 Gln Asp Phe Gly Phe Ser Val Glu Lys Cys Ser Lys Gln Leu Lys Ser
 50 55 60

65 Asn Ile Asn Ile Arg Phe Gly Ile Ile Leu Arg Glu Asp Ile Lys Glu
 65 70 75 80

70 Leu Phe Leu Asp Leu Ala Leu Met Ser Gln Gly Ser Ser Val Leu Asn
 85 90 95

75 Phe Ser Tyr Pro Ile Cys Glu Ala Ala Leu Pro Lys Phe Ser Phe Cys
 100 105 110

SUBSTITUTE SHEET (rule 26)

61

5 Gly Arg Arg Lys Gly Glu Gln Ile Tyr Tyr Ala Gly Pro Val Asn Asn
 115 120 125
 Pro Glu Phe Thr Ile Pro Gln Gly Glu Tyr Gln Val Leu Leu Glu Leu
 130 135 140
 10 Tyr Thr Glu Lys Arg Ser Thr Val Ala Cys Ala Asn Ala Thr Ile Met
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 Cys Ser
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 tgc aac tca tcc gat gca agt att tca tac acc tac tgt gat aaa atg 96
 35 Cys Asn Ser Ser Asp Ala Ser Ile Ser Tyr Thr Tyr Cys Asp Lys Met
 20 25 30
 caa tac cca att tca att aat gtt aac ccc tgt ata gaattgaaag 142
 40 Gln Tyr Pro Ile Ser Ile Asn Val Asn Pro Cys Ile
 35 40
 gatccaaagg attattgcac attttctaca ttccaaggag agatttaaag caattatatt 202
 tcaatctcta tataactgtc aacaccatga atcttccaaa gcgcaaagaa gttatttgcc 262
 45 gaggatctga tgacgattac tctttttgca gagctctgaa gggagagact gtgaatacaa 322
 caatatcatt ctcttcaag ggaataaaat tttctaaggg aaaatacaaa tgtgttggtg 382
 50 aagctatttc tgggagccca gaagaaatgc tcttttgctt ggagtttgtc atcctacacc 442
 aacctaattc aaattagaat aaattgagta tttaaaaaaa aaaa 486
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 60 <400> 44
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 1 5 10 15

SUBSTITUTE SHEET (rule 26)

62

5 Cys Asn Ser Ser Asp Ala Ser Ile Ser Tyr Thr Tyr Cys Asp Lys Met
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Gln Tyr Pro Ile Ser Ile Asn Val Asn Pro Cys Ile
35 40

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<212> DNA
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1 5 10 15

30 gaa gct cag aag cag tat tgg gtc tgc aac tca tcc gat gca agt att 96
Glu Ala Gln Lys Gln Tyr Trp Val Cys Asn Ser Ser Asp Ala Ser Ile
20 25 30

35 tca tac acc tac tgt gat aaa atg caa tac cca att tca att aat gtt 144
Ser Tyr Thr Tyr Cys Asp Lys Met Gln Tyr Pro Ile Ser Ile Asn Val
35 40 45

40 aac ccc tgt ata gaa ttg aaa gga tcc aaa gga tta ttg cac att ttc 192
Asn Pro Cys Ile Glu Leu Lys Gly Ser Lys Gly Leu Leu His Ile Phe
50 55 60

40 tac att cca agg aga gat tta aag caa tta tat ttc aat ctc tat ata 240
Tyr Ile Pro Arg Arg Asp Leu Lys Gln Leu Tyr Phe Asn Leu Tyr Ile
65 70 75 80

45 act gtc aac acc atg aat ctt cca aag cgc aaa gaa gtt att tgc cga 288
Thr Val Asn Thr Met Asn Leu Pro Lys Arg Lys Glu Val Ile Cys Arg
85 90 95

50 gga tct gat gac gat tac tct ttt tgc aga gct ctg aag gga gag act 336
Gly Ser Asp Asp Asp Tyr Ser Phe Cys Arg Ala Leu Lys Gly Glu Thr
100 105 110

55 gtg aat aca aca ata tca ttc tcc ttc aag gga ata aaa ttt tct aag 384
Val Asn Thr Thr Ile Ser Phe Ser Phe Lys Gly Ile Lys Phe Ser Lys
115 120 125

60 gga aaa tac aaa tgt gtt gtt gaa gct att tct ggg agc cca gaa gaa 432
Gly Lys Tyr Lys Cys Val Val Glu Ala Ile Ser Gly Ser Pro Glu Glu
130 135 140

atg ctc ttt tgc ttg gag ttt gtc atc cta cac caa cct aat tca aat 480
Met Leu Phe Cys Leu Glu Phe Val Ile Leu His Gln Pro Asn Ser Asn
145 150 155 160

tag 483

SUBSTITUTE SHEET (rule 26)

63

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15 Glu Ala Gln Lys Gln Tyr Trp Val Cys Asn Ser Ser Asp Ala Ser Ile
 20 25 30

Ser Tyr Thr Tyr Cys Asp Lys Met Gln Tyr Pro Ile Ser Ile Asn Val
 35 40 45

20 Asn Pro Cys Ile Glu Leu Lys Gly Ser Lys Gly Leu Leu His Ile Phe
 50 55 60

Tyr Ile Pro Arg Arg Asp Leu Lys Gln Leu Tyr Phe Asn Leu Tyr Ile
 65 70 75 80

25 Thr Val Asn Thr Met Asn Leu Pro Lys Arg Lys Glu Val Ile Cys Arg
 85 90 95

30 Gly Ser Asp Asp Asp Tyr Ser Phe Cys Arg Ala Leu Lys Gly Glu Thr
 100 105 110

Val Asn Thr Thr Ile Ser Phe Ser Phe Lys Gly Ile Lys Phe Ser Lys
 115 120 125

35 Gly Lys Tyr Lys Cys Val Val Glu Ala Ile Ser Gly Ser Pro Glu Glu
 130 135 140

Met Leu Phe Cys Leu Glu Phe Val Ile Leu His Gln Pro Asn Ser Asn
 145 150 155 160

40 <210> 47
 <211> 498
 <212> DNA
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45 <220>
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50 <220>
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 <222> (53)..(394)

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 Met Leu
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60 cca ttt att ctc ttt tcg acg ctg ctt tct ccc ata ttg act gaa tct 106
 Pro Phe Ile Leu Phe Ser Thr Leu Leu Ser Pro Ile Leu Thr Glu Ser
 5 10 15

gag aag caa cag tgg ttc tgc aac tcc tcc gat gca att att tcc tac 154

SUBSTITUTE SHEET (rule 26)

5	Glu 20	Lys 20	Gln 20	Trp 20	Phe 25	Cys 25	Asn 25	Ser 25	Ser 25	Asp 30	Ala 30	Ile 30	Ile 30	Ser 30	Tyr 30		
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	Ser	Tyr	Cys	Asp	His	Leu	Lys	Phe	Pro	Ile	Ser	Ile	Ser	Ser	Glu	Pro	
	35					40					45					50	
10	tgc	ata	aga	ctg	agg	gga	acc	aat	gga	ttt	gtg	cat	gtt	gag	ttc	att	250
	Cys	Ile	Arg	Leu	Arg	Gly	Thr	Asn	Gly	Phe	Val	His	Val	Glu	Phe	Ile	
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15	cca	aga	gga	aac	tta	aaa	tat	tta	tat	ttc	aac	cta	ttc	atc	agt	gtc	298
	Pro	Arg	Gly	Asn	Leu	Lys	Tyr	Leu	Tyr	Phe	Asn	Leu	Phe	Ile	Ser	Val	
				70					75					80			
20	aac	tcc	ata	gag	ttg	ccg	aag	cgt	aag	gaa	gtt	ctg	tgc	cat	gga	cat	346
	Asn	Ser	Ile	Glu	Leu	Pro	Lys	Arg	Lys	Glu	Val	Leu	Cys	His	Gly	His	
			85					90					95				
25	gat	gat	gac	tat	tct	ttt	tgc	aga	gct	ctg	aaa	gga	gga	tat	gct	att	394
	Asp	Asp	Asp	Tyr	Ser	Phe	Cys	Arg	Ala	Leu	Lys	Gly	Gly	Tyr	Ala	Ile	
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40	Glu	Ser	Glu	Lys	Gln	Gln	Trp	Phe	Cys	Asn	Ser	Ser	Asp	Ala	Ile	Ile	
				20					25					30			
45	Ser	Tyr	Ser	Tyr	Cys	Asp	His	Leu	Lys	Phe	Pro	Ile	Ser	Ile	Ser	Ser	
			35					40					45				
	Glu	Pro	Cys	Ile	Arg	Leu	Arg	Gly	Thr	Asn	Gly	Phe	Val	His	Val	Glu	
		50					55					60					
50	Phe	Ile	Pro	Arg	Gly	Asn	Leu	Lys	Tyr	Leu	Tyr	Phe	Asn	Leu	Phe	Ile	
	65					70					75					80	
	Ser	Val	Asn	Ser	Ile	Glu	Leu	Pro	Lys	Arg	Lys	Glu	Val	Leu	Cys	His	
					85					90					95		
55	Gly	His	Asp	Asp	Asp	Tyr	Ser	Phe	Cys	Arg	Ala	Leu	Lys	Gly	Gly	Tyr	
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SUBSTITUTE SHEET (rule 26)

65

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<213> Unknown

<220>

<223> Description of Unknown Organism:primate

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20 25 30

Ser Tyr Ser Tyr Cys Asp His Leu Lys Phe Pro Ile Ser Ile Ser Ser
35 40 45

20 Glu Pro Cys Ile Arg Leu Arg Gly Thr Asn Gly Phe Val His Val Glu
50 55 60

Phe Ile Pro Arg Gly Asn Leu Lys Tyr Leu Tyr Phe Asn Leu Phe Ile
65 70 75 80

25 Ser Val Asn Ser Ile Glu Leu Pro Lys Arg Lys Glu Val Leu Cys His
85 90 95

30 Gly His Asp Asp Asp Tyr Ser Phe Cys Arg Ala Leu Lys Gly Glu Thr
100 105 110

Val Asn Thr Ser Ile Pro Phe Ser Phe Glu Gly Ile Leu Phe Pro Lys
115 120 125

35 Gly His Tyr Arg Cys Val Ala Glu Ala Ile Ala Gly Asp
130 135 140

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<212> PRT
<213> Unknown

<220>

45 <223> Description of Unknown Organism:rodent

<400> 50

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1 5 10 15

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20 25 30

55 Cys Asn Ser Gly Gly Leu Glu Val Val Tyr Gln Ser Cys Asp Pro Leu
35 40 45

Gln Asp Phe Gly Leu Ser Ile Asp Gln Cys Ser Lys Gln Ile Gln Ser
50 55 60

60 Asn Leu Asn Ile Arg Phe Gly Ile Ile Leu Arg Gln Asp Ile Arg Lys
65 70 75 80

Leu Phe Leu Asp Ile Thr Leu Met Ala Lys Gly Ser Ser Ile Leu Asn
85 90 95

SUBSTITUTE SHEET (rule 26)

67

5 aaa gaa atc cca cag cga gat tac act atc aca gca agg ctg act aac 433
 Lys Glu Ile Pro Gln Arg Asp Tyr Thr Ile Thr Ala Arg Leu Thr Asn
 130 135 140

10 gaa gat cgc gcc act gtt gct tgt gct gat ttt acc gtg aaa aat tat 481
 Glu Asp Arg Ala Thr Val Ala Cys Ala Asp Phe Thr Val Lys Asn Tyr
 145 150 155

15 tta gat tat taagcaaaac aacgcactcg gtccgactcc cttaaaacta 530
 Leu Asp Tyr
 160

20 cagattccta aaactattca agcccagtga gctgcttgca tgcttcagtg attctgaagg 590
 aaagatctcc cgcacggtgg ttctgatgct gttcctcttc gtaattcaac ttttttggag 650
 aagtcactag gccctaccct ctagtggttaa ttttatctcc aaatgcactc tgtagcccac 710
 ttttcgcttt taatatatac agctgcaaat agaaagtatt tgataccaac attctcatct 770

25 caggatgaaa atagtacaaa gcagaagagg cgagagccaa aacagatttt tgcagtaagc 830
 tatggaggta tccatttcta acacaagcta aagaagattg tcatatgtat tatgcagtta 890
 tagcactcaa ctttttcagt ttttcacaag gcctgtttgg agcctccatt ggtataaatt 950

30 ttgttgtaac cacagaacaa agaccaaata ggatgaacat ggctccatgt tcagtcactc 1010
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35 ttacagtgat gtgagaatcc ttttgtttaa gctacatgct gttcccgctt gtcaataaat 1130
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40 <210> 52
 <211> 160
 <212> PRT
 <213> Unknown

45 <400> 52
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 20 25 30

 Leu Glu Ile Tyr Tyr Lys Ser Cys Asp Pro Gln Gln Asp Phe Ala Phe
 35 40 45

55 Ser Ile Asp Arg Cys Ser Asp Val Thr Thr His Thr Phe Asp Ile Arg
 50 55 60

 Ala Ala Met Val Leu Arg Gln Ser Ile Lys Glu Leu Tyr Ala Lys Val
 65 70 75 80

60 Asp Leu Ile Ile Asn Gly Lys Thr Val Leu Ser Tyr Ser Glu Thr Leu
 85 90 95

SUBSTITUTE SHEET (rule 26)

68

5 Cys Gly Pro Gly Leu Ser Lys Leu Ile Phe Cys Gly Lys Lys Lys Gly.
 100 105 110
 Glu His Leu Tyr Tyr Glu Gly Pro Ile Thr Leu Gly Ile Lys Glu Ile
 115 120 125
 10 Pro Gln Arg Asp Tyr Thr Ile Thr Ala Arg Leu Thr Asn Glu Asp Arg
 130 135 140
 Ala Thr Val Ala Cys Ala Asp Phe Thr Val Lys Asn Tyr Leu Asp Tyr
 145 150 155 160
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 35 agt agc cgt tta caa gct aag cag cag ccc cag ccc agc cag acg gaa 104
 Ser Ser Arg Leu Gln Ala Lys Gln Gln Pro Gln Pro Ser Gln Thr Glu
 5 10 15 20
 tcc ccc caa gaa gcc cag ata atc cag gcc aag aag agg aaa act acc 152
 Ser Pro Gln Glu Ala Gln Ile Ile Gln Ala Lys Lys Arg Lys Thr Thr
 40 25 30 35
 cag gat gtc aaa aaa aga aga gag gag gtc acc aag aaa cat cag tat 200
 Gln Asp Val Lys Lys Arg Arg Glu Glu Val Thr Lys Lys His Gln Tyr
 40 45 50
 45 gaa att agg aat tgt tgg cca cct gta tta tct ggg ggg atc agt cct 248
 Glu Ile Arg Asn Cys Trp Pro Pro Val Leu Ser Gly Gly Ile Ser Pro
 55 60 65
 50 tgc att atc att gaa aca cct cac aaa gaa ata gga aca agt gat ttc 296
 Cys Ile Ile Ile Glu Thr Pro His Lys Glu Ile Gly Thr Ser Asp Phe
 70 75 80
 tcc aga ttt aca aat tac aga ttt aaa aat ctt ttt att aat cct tca 344
 Ser Arg Phe Thr Asn Tyr Arg Phe Lys Asn Leu Phe Ile Asn Pro Ser
 85 90 95 100
 cct ttg cct gat tta agc tgg gga tgt tca aaa gaa gtc tgg cta aac 392
 Pro Leu Pro Asp Leu Ser Trp Gly Cys Ser Lys Glu Val Trp Leu Asn
 60 105 110 115
 atg tta aaa aag gag agc aga tat gtt cat gac aaa cat ttt gaa gtt 440
 Met Leu Lys Lys Glu Ser Arg Tyr Val His Asp Lys His Phe Glu Val
 120 125 130

SUBSTITUTE SHEET (rule 26)

69

5	ctg cat tct gac ttg gaa cca cag atg agg tcc ata ctt cta gac tgg	488
	Leu His Ser Asp Leu Glu Pro Gln Met Arg Ser Ile Leu Leu Asp Trp	
	135 140 145	
10	ctt tta gag gta tgt gaa gta tac aca ctt cat agg gaa aca ttt tat	536
	Leu Leu Glu Val Cys Glu Val Tyr Thr Leu His Arg Glu Thr Phe Tyr	
	150 155 160	
15	ctt gca caa gac ttt ttt gat aga ttt atg ttg aca caa aag gat ata	584
	Leu Ala Gln Asp Phe Phe Asp Arg Phe Met Leu Thr Gln Lys Asp Ile	
	165 170 175 180	
	aat aaa aat atg ctt caa ctc att gga att acc tca tta ttc att gct	632
	Asn Lys Asn Met Leu Gln Leu Ile Gly Ile Thr Ser Leu Phe Ile Ala	
	185 190 195	
20	tcc aaa ctt gag gaa atc tat gct cct aaa ctc caa gag ttt gct tac	680
	Ser Lys Leu Glu Glu Ile Tyr Ala Pro Lys Leu Gln Glu Phe Ala Tyr	
	200 205 210	
25	gtc act gat ggt gct tgc agt gaa gaa gat atc tta agg atg gaa ctc	728
	Val Thr Asp Gly Ala Cys Ser Glu Glu Asp Ile Leu Arg Met Glu Leu	
	215 220 225	
30	att ata tta aag gct tta aaa tgg gaa ctt tgt cct gta aca atc atc	776
	Ile Ile Leu Lys Ala Leu Lys Trp Glu Leu Cys Pro Val Thr Ile Ile	
	230 235 240	
35	tcc tgg cta aat ctc ttt ctc caa gtt gat gct ctt aaa gat gct cct	824
	Ser Trp Leu Asn Leu Phe Leu Gln Val Asp Ala Leu Lys Asp Ala Pro	
	245 250 255 260	
	aaa gtt ctt cta cct cag tat tct cag gaa aca ttc att caa ata gct	872
	Lys Val Leu Leu Pro Gln Tyr Ser Gln Glu Thr Phe Ile Gln Ile Ala	
	265 270 275	
40	cag ctt tta gat ctg tgt att cta gcc att gat tca tta gag ttc cag	920
	Gln Leu Leu Asp Leu Cys Ile Leu Ala Ile Asp Ser Leu Glu Phe Gln	
	280 285 290	
45	tac aga ata ctg act gct gct gcc ttg tgc cat ttt acc tcc att gaa	968
	Tyr Arg Ile Leu Thr Ala Ala Ala Leu Cys His Phe Thr Ser Ile Glu	
	295 300 305	
50	gtg gtt aag aaa gcc tca ggt ttg gag tgg gac agt att tca gaa tgt	1016
	Val Val Lys Lys Ala Ser Gly Leu Glu Trp Asp Ser Ile Ser Glu Cys	
	310 315 320	
55	gta gat tgg atg gta cct ttt gtc aat gta gta aaa agt act agt cca	1064
	Val Asp Trp Met Val Pro Phe Val Asn Val Val Lys Ser Thr Ser Pro	
	325 330 335 340	
	gtg aag ctg aag act ttt aag aag att cct atg gaa gac aga cat aat	1112
	Val Lys Leu Lys Thr Phe Lys Lys Ile Pro Met Glu Asp Arg His Asn	
	345 350 355	
60	atc cag aca cat aca aac tat ttg gct atg ctg gag gaa gta aat tac	1160
	Ile Gln Thr His Thr Asn Tyr Leu Ala Met Leu Glu Glu Val Asn Tyr	
	360 365 370	

SUBSTITUTE SHEET (rule 26)

5	ata aac acc ttc aga aaa ggg gga cag ttg tca cca gtg tgc aat gga	1208
	Ile Asn Thr Phe Arg Lys Gly Gln Leu Ser Pro Val Cys Asn Gly	
	375 380 385	
10	ggc att atg aca cca ccg aag agc act gaa aaa cca cca gga aaa cac	1256
	Gly Ile Met Thr Pro Pro Lys Ser Thr Glu Lys Pro Pro Gly Lys His	
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72

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73

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75

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification: C12N 15/12, 15/19, 15/57, 15/62, C07K 16/18, 16/28, 16/24, 16/40, C12Q 1/68, G01N 33/566, 33/68, A61K 38/17, 38/19, 38/48	A3	(11) International Publication Number: WO 00/01817 (43) International Publication Date: 13 January 2000 (13.01.00)																		
(21) International Application Number: PCT/US99/12366 (22) International Filing Date: 6 July 1999 (06.07.99) (30) Priority Data: <table border="0"> <tr> <td>09/110,938</td> <td>6 July 1998 (06.07.98)</td> <td>US</td> </tr> <tr> <td>09/114,466</td> <td>13 July 1998 (13.07.98)</td> <td>US</td> </tr> <tr> <td>60/093,897</td> <td>23 July 1998 (23.07.98)</td> <td>US</td> </tr> <tr> <td>09/132,968</td> <td>12 August 1998 (12.08.98)</td> <td>US</td> </tr> <tr> <td>09/136,214</td> <td>18 August 1998 (18.08.98)</td> <td>US</td> </tr> <tr> <td>60/099,999</td> <td>11 September 1998 (11.09.98)</td> <td>US</td> </tr> </table> (71) Applicant: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US). (72) Inventors: BATES, Elizabeth, Esther, Mary; 4, place Gabriel Rambaud, F-69001 Lyon (FR). LEBECQUE, Serge, J., E.; 514, Chemin du Marand, F-69380 Civrieux d'Azergue (FR). MURPHY, Erin, E.; 180 Emerson Street, Palo Alto, CA 94301 (US). MATTSON, Jeanine, D.; 559 Alvarado Street, San Francisco, CA 94114 (US). GORMAN, Daniel, M.; 6371 Central Avenue, Newark, CA 94560 (US). HEDRICK, Joseph, A.; 52-08 Quail Ridge Drive, Plainsboro, NJ 08536 (US). WANG, Luquan; 21 Hollis Road, East Brunswick,		09/110,938	6 July 1998 (06.07.98)	US	09/114,466	13 July 1998 (13.07.98)	US	60/093,897	23 July 1998 (23.07.98)	US	09/132,968	12 August 1998 (12.08.98)	US	09/136,214	18 August 1998 (18.08.98)	US	60/099,999	11 September 1998 (11.09.98)	US	NJ 08816 (US). ZLOTNIK, Albert; 507 Alger Drive, Palo Alto, CA 94306 (US). MURGOLO, Nicholas, J.; 99 Rolling Hill Drive, Millington, NJ 07946 (US). GREENE, Jonathan, R.; 457 Tillou Road, South Orange, NJ 07079 (US). JOHNSTON, James, A.; 205 Mary Alice Drive, Los Gatos, CA 95032 (US). BAZAN, Jose, Fernando; 775 University Drive, Menlo Park, CA 94025 (US). MAHONY, Daniel; 330 East 39th Street #21-A, New York, NY 10016 (US). LEES, Emma, M.; 3107 Washington Street, San Francisco, CA 94115 (US). (74) Agents: THAMPOE, Immac, J. et al.; Schering-Plough Corporation, Patent Dept., K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MD, MG, MK, MN, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> (88) Date of publication of the international search report: 29 June 2000 (29.06.00)
09/110,938	6 July 1998 (06.07.98)	US																		
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09/132,968	12 August 1998 (12.08.98)	US																		
09/136,214	18 August 1998 (18.08.98)	US																		
60/099,999	11 September 1998 (11.09.98)	US																		
(54) Title: MAMMALIAN GENES; DENDRITIC CELL PROSTAGLANDIN-LIKE TRANSPONDER (DC-PGT), HDTEA84, HSLJD37R AND RANKL, HCC5 CHEMOKINE, DEUBIQUITINATING 11 AND 12 (DUB11, DUB12), MD-1, MD2 AND CYCLIN E2, RELATED REAGENTS AND METHODS (57) Abstract <p>Purified genes from a mammal, reagents related thereto including purified proteins, specific antibodies, and nucleic acids encoding the polypeptides are provided. Methods of using said reagents and diagnostic kits are also provided. Characterization of genes and products relating to DC-PGT (Dendritic cell prostaglandin-like transporter), HDTEA84, HSLJD37R and RANKL (related to TNF receptor family), HCC5 chemokine, Dub 11 and Dub 12 (Deubiquitinating 11 and 12), MD-1 and MD-2 (proteins which exhibit properties of ligands for proteins exhibiting a leucine-rich protein motif (LRR)) and cyclin E2.</p>																				

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EE	Estonia						

INTERNATIONAL SEARCH REPORT

International Application No

PCT, US 99/12366

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/12 C12N15/19 C12N15/57 C12N15/62 C07K16/18
 C07K16/28 C07K16/24 C07K16/40 C12Q1/68 G01N33/566
 G01N33/68 A61K38/17 A61K38/19 A61K38/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K C12N C12Q G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>R. LU ET AL.: "Cloning, In vitro expression, and tissue distribution of a human Prostaglandin transporter cDNA (hPGT)."</p> <p>THE JOURNAL OF CLINICAL INVESTIGATION, vol. 98, no. 5, 1 September 1996 (1996-09-01), pages 1142-1149, XP000863207 cited in the application the whole document</p> <p style="text-align: center;">--- -/--</p>	1-22



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* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

7 January 2000

Date of mailing of the international search report

26.04.00

Name and mailing address of the ISA

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Authorized officer

Hix, R

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/12366

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	D.L. LACEY ET AL.: "Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation." CELL, vol. 93, 17 April 1998 (1998-04-17), pages 165-176, XP002125264 cited in the application the whole document ---	
A	LODI P J ET AL: "HIGH-RESOLUTION SOLUTION STRUCTURE OF THE BETA CHEMOKINE HMIP-1BETABY MULTIDIMENSIONAL NMR" SCIENCE,US,AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, vol. 263, page 1762-1767 XP002054455 ISSN: 0036-8075 cited in the application the whole document ---	
A	WO 96 34891 A (HUMAN GENOME SCIENCES INC) 7 November 1996 (1996-11-07) cited in the application the whole document ---	
A	WO 95 17092 A (HUMAN GENOME SCIENCES INC) 29 June 1995 (1995-06-29) cited in the application the whole document ---	
A	HOCHSTRASSER M: "UBIQUITIN, PROTEASOMES, AND THE REGULATION OF INTRACELLULAR PROTEINDEGRADATION" CURRENT OPINION IN CELL BIOLOGY,GB,CURRENT SCIENCE, LONDON, vol. 7, no. 2, page 215-223 XP000670260 ISSN: 0955-0674 cited in the application the whole document ---	
A	K. MIYAKE ET AL.: "Mouse MD-1, a molecule that is physically associated with RP105 and positively regulates its expression." THE JOURNAL OF IMMUNOLOGY, vol. 161, 1998, pages 1348-1353, XP002125265 cited in the application the whole document ---	

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/12366

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LEW D J ET AL: "ISOLATION OF THREE NOVEL HUMAN CYCLINS BY RESCUE OF G1 CYCLIN (CLN) FUNCTION IN YEAST" CELL,US,CELL PRESS, CAMBRIDGE, NA, vol. 66, 20 September 1991 (1991-09-20), page 1197-1206 XP002039130 ISSN: 0092-8674 cited in the application the whole document	
P,Y	--- US 5 792 851 A (SCHUSTER VICTOR L ET AL) 11 August 1998 (1998-08-11) the whole document	1-22
Y	--- NAGASE ET AL: "Prediction of the coding sequences of unidentified human genes. XII. The complete sequences of 100 new cDNA clones from brain which code for large proteins in vitro" DNA RESEARCH,JP,UNIVERSAL ACADEMY PRESS, vol. 5, no. 5, page 355-364-64 XP002111974 ISSN: 1340-2838 the whole document	1-22
Y	--- N. KANAI ET AL.: "Identification and characterization of a Prostaglandin transporter." SCIENCE, vol. 268, 12 May 1995 (1995-05-12), pages 866-869, XP002125266 cited in the application the whole document	1-22
Y	--- R. LU ET AL.: "Molecular cloning of the gene for human Prostaglandin Transporter hPGT: gene organization, promoter activity, and chromosomal localization." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 246, 1998, pages 805-812, XP002125267 the whole document -----	1-22

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/12366

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Claims 1-22

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-22

An isolated or recombinant polypeptide comprising segments with identity to SEQ ID NO: 2 and polynucleotides which hybridize to the coding portion of SEQ ID NO:1, fusion proteins, pharmaceutical compositions thereof, vectors comprising said polynucleotide and methods of identifying compounds that bind to said polypeptide, designated Dendritic cell prostaglandin-like transporter (DC-PGT).

2. Claims: 23-42 (partly)

Isolated or recombinant polynucleotide encoding antigenic polypeptides comprising at least 17 contiguous amino acids from SEQ ID NO: 6 encoding structural motifs characteristic of a member of the TNF receptor family designated HDTEA84 and polynucleotides which hybridise to the coding portions of SEQ ID NO: 5, expression vectors comprising said polynucleotides, and binding compounds comprising an antibody binding site which binds to said polypeptides and detection kits comprising said binding compound.

3. Claims: 23-42 (partly)

Isolated or recombinant polynucleotide encoding antigenic polypeptides comprising at least 17 contiguous amino acids from SEQ ID NO: 8 and 10 encoding structural motifs characteristic of a member of the TNF receptor family, designated HSLJD37R and polynucleotides which hybridise to the coding portions of SEQ ID NO: 7 and 9 expression vectors comprising said polynucleotides, and binding compounds comprising an antibody binding site which binds to said polypeptides and detection kits comprising said binding compound.

4. Claims: 23-42 (partly)

Isolated or recombinant polynucleotide encoding antigenic polypeptides comprising at least 17 contiguous amino acids from SEQ ID NO: 17, 19, 21, 23 encoding structural motifs characteristic of a member of the TNF receptor family, designated RANKL and polynucleotides which hybridise to the coding portions of SEQ ID NO: 16, 18, 20 and 22, expression vectors comprising said polynucleotides, and binding compounds comprising an antibody binding site which binds to said polypeptides and detection kits comprising said binding compound.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

5. Claims: 43-63 (partly)

Recombinant HCC5 polypeptide with identity over a length of at least 12 amino acids to SEQ ID NO: 25, an isolated natural sequence and fusion proteins and compositions thereof

6. Claims: 43-63 (partly)

Recombinant Dub11 polypeptide with identity over a length of at least 12 amino acids to SEQ ID NO: 32 or 34, an isolated natural sequence and fusion proteins and compositions thereof

7. Claims: 43-63 (partly)

Recombinant Dub12 polypeptide with identity over a length of at least 12 amino acids to SEQ ID NO: 36 or 38, an isolated natural sequence and fusion proteins and compositions thereof

8. Claims: 43-63 (partly)

Recombinant MD-1 polypeptide with identity over a length of at least 12 amino acids to SEQ ID NO: 42, an isolated natural sequence and fusion proteins and compositions thereof

9. Claims: 43-63 (partly)

Recombinant primate MD-2 polypeptide with identity over a length of at least 12 amino acids to SEQ ID NO: 44 or 46, an isolated natural sequence and fusion proteins and compositions thereof

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

10. Claims: 43-63 (partly)

Recombinant rodent MD-2 polypeptide with identity over a length of at least 12 amino acids to SEQ ID NO: 48 or 49, an isolated natural sequence and fusion proteins and compositions thereof

11. Claims: 64-84

Isolated or recombinant polypeptide encoding at least 17 contiguous amino acid residues of SEQ ID NO: 54, kits comprising said polypeptide, methods of using said polypeptide in the evaluation of the selective binding of a compound to cyclin E2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/12366

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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